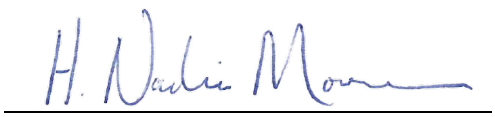
EXHIBIT 51

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16 -2738 (FLW) (LHG)**

RULE 26 REPORT OF
H. NADIA MOORE, PH.D., DABT, ERT



H. Nadia Moore, Ph.D., DABT, ERT
Principal Toxicologist

February 25, 2019

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A. SUMMARY OF PRIMARY OPINIONS

I was asked to provide an expert opinion as a toxicologist regarding alleged adverse health effects from exposure to Johnson's Baby Powder and Shower to Shower. I have also been asked to respond to plaintiffs' expert reports, focusing on those submitted by Drs. Carson, Crowley, Longo, Plunkett and Zelikoff, because they all touch on my field of toxicology.

My primary opinions regarding potential adverse health effects from exposure to Johnson's Baby Powder and Shower to Shower talcum powder products are as follows:

1. Cosmetic talc

- Scientific literature does not support a causal relationship between perineal talc use and ovarian cancer.

2. Asbestos

- Scientific studies do not support the theory that asbestos, as an alleged contaminant in talc, causes ovarian cancer in women.
- Regulations that ensure asbestos levels will protect people from asbestos-related mesothelioma will also protect people from any asbestos-related ovarian cancer.
- If talcum products contained asbestos fibers at the maximum level alleged by Drs. Longo and Rigler, concentrations would not be significant or meaningful to human health; exposure estimation using conservative assumptions of all other factors (use, frequency, duration) results in 50-year cumulative airborne asbestos fiber exposures that are three times below those associated with ambient, background exposure; at least 4,000 times below those derived working for 50 years at the OSHA PEL; and at least 29,000 times below tremolite asbestos levels considered protective of mesothelioma.
- This analysis supports the conclusion that scientific studies do not show that asbestos, as an alleged contaminant in talc, causes ovarian cancer in women.

3. Chromium

- No association has been found between chromium and ovarian cancer in humans or animals.
- Carcinogenic propensity of chromium is very different depending on the valence state (i.e., charge) of the chromium ion considered. Chromium(III), commonly found in rocks, is not associated with cancer. Chromium(VI), the formation of which is associated with industrial processes, has been shown to be a carcinogen with high occupational exposures of airborne chromium(VI) associated with increased risk of respiratory (lung) cancer (but not dermal).
- There are no scientific data supporting the concept that alleged trace levels of chromium in talc products cause ovarian cancer.

4. Cobalt

- No association has been found between cobalt and ovarian cancer in humans or animals.

- The allegation that a trace level of cobalt can cause ovarian cancer is not consistent with established scientific knowledge. Cobalt is an essential metal, and its intake is required for human health.
- There are no scientific data supporting the concept that alleged trace levels of cobalt cause ovarian cancer.

5. Nickel

- No association has been found between exposure to nickel and ovarian cancer in humans or animals.
- No conclusions can be drawn regarding the carcinogenicity and/or the carcinogenic potency of nickel from talc (on any organ) without knowledge of the specific bioavailability of nickel from talc.
- The allegation that a trace level of nickel can cause ovarian cancer is not consistent with established scientific knowledge; the US Food & Drug Administration (FDA) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have both established daily exposure levels that are protective of the public health for all patient populations.
- There are no scientific data supporting the concept that alleged trace levels of nickel in talc products cause ovarian cancer.

6. Fragrances

- Scientific data do not support the concept that fragrance ingredients used in Johnson's Baby Powder or Shower to Shower products cause ovarian cancer.

7. Additional concerns regarding plaintiffs' experts' opinions

- Fundamental toxicology-based concerns
  - i) Dr. Plunkett confuses elements of a risk assessment and her assertion that assessment of causation is not part of human health risk assessment is not consistent with generally accepted methods used by toxicologists.
  - ii) Because Dr. Plunkett did not consider the nature and magnitude of doses associated with human risk, her analysis was not conducted pursuant to a generally accepted scientific methodology.
  - iii) Because Dr. Carson did not consider the nature and magnitude of doses associated with human risk, his analysis was not conducted pursuant to a generally accepted scientific methodology.
  - iv) Dr. Plunkett's grouping of all chemicals with carcinogenic hazards together is not consistent with generally accepted methods used by toxicologists.
  - v) Dr. Crowley's assertion that effects from fragrance ingredients are likely additive to the alleged risks of ovarian cancer is not consistent with generally accepted methods used by toxicologists.

  - vi) Dr. Zelikoff's method for assessing biological plausibility is scientifically flawed and not a generally accepted scientific methodology.
  - vii) Multiple plaintiffs' experts omit the use of Bradford Hill causation criteria or apply the criteria without critical review in a manner not consistent with generally accepted methods.

- Science-based concerns
  - i) Opinions by some of plaintiffs' experts that any exposure to a carcinogen can cause cancer are not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.
  - ii) Dr. Crowley's opinion that positive genotoxicity assays (specifically CHO assays) provide an animal model of support for increased risk of ovarian cancer is not consistent with generally accepted methods used by toxicologists.
  - iii) Dr. Crowley misrepresented both study outcome and the FDA's ruling in his statement regarding benzophenone.
  - iv) Methods used by Dr. Saed to generate data presented in his report and manuscript were flawed and unreliable and therefore preclude any conclusion regarding the activity of talc with the studied cells.

- Literature-based concerns
  - i) Dr. Zelikoff's use of data of unknown quality to inform her opinions is methodologically flawed and not generally accepted by the scientific community.
  - ii) Dr. Zelikoff's method of copying hazard-identification statements directly (or with a few word changes) without attribution of the author is not a generally accepted scientific methodology.
  - iii) Dr. Zelikoff's method of copying and pasting incomplete information is misleading and not a generally accepted scientific methodology.
  - iv) Dr. Zelikoff's method of copying and pasting presents outdated information as current scientific knowledge and is misleading and not a generally accepted scientific methodology.

B. QUALIFICATIONS

I am a Principal Toxicologist at Veritox, Inc., in Redmond, Washington. I have more than 25 years of multidisciplinary experience in toxicology, regulatory compliance, molecular, biology and analytical chemistry.

I am certified in toxicology as a Diplomate of the American Board of Toxicology and am admitted to both the United Kingdom and EUROTOX registries as a European Registered Toxicologist. I am an associate member of the American College of Occupational and Environmental Medicine, member of the Society of Toxicology, American College of Toxicology, British Toxicology Society, American Association for the Advancement of Science,

American Conference of Governmental Industrial Hygienists, American Chemical Society, American Industrial Hygiene Association, and Society for Experimental Biology and Medicine. I currently serve on the Awards Committee of the Women in Toxicology Specialty Interest Group for the Society of Toxicology and as President for the Pacific Northwest Association of Toxicologists (PANWAT). Previously, I served as Councilor for the Pacific Northwest Association of Toxicologists.

I received a Bachelor of Science degree in Chemistry (biochemistry emphasis) with *cum laude* honors from Pacific Lutheran University and a Ph.D. in Environmental Toxicology from the University of Washington, School of Public Health and Community Medicine, Department of Environmental Health and Occupational Health Sciences.

Following completion of my undergraduate degree, I joined an analytical chemistry group at Battelle Memorial Institute ("Battelle"), primarily supporting laboratory animal inhalation studies. During my nine-year tenure, I was responsible for method development, validation, and implementation of methods to determine test article purity and test article concentration within exposure atmospheres. I was also responsible for developing methods to quantitate test articles and/or metabolite concentrations in biological samples for governmental (National Toxicology Program) and industrial (e.g., pharmaceutical) clients. In 2001, I transferred to a health protection group and prepared risk-based toxicology reports for single compounds, chemical classes and complex mixtures until 2003, when I successfully applied for and was granted an educational leave to pursue graduate study in toxicology. My dissertation at the University of Washington focused on mechanisms underlying the developmental neurotoxicity of ethanol.

I returned to Battelle's inhalation laboratory as a toxicologist and study director after obtaining my Ph.D. In this role, my responsibilities included study design; scientific, technical, and procedural oversight of all study phases; and the overall conduct, interpretation, and reporting of studies, including review and evaluation of all scientific literature and data available for inclusion in study design or result interpretation. In addition, I consulted with Battelle's industrial hygienist to derive and/or establish acceptable exposure levels for staff working with or near studied compounds, which were primarily selected for testing due to a lack of available inhalation toxicity data.

In January 2011, the Chief Executive Officer of Battelle Memorial Institute, Jeffrey Wadsworth, appointed me to the Institutional Animal Care and Use Committee (IACUC) serving Pacific Northwest National Laboratory, Sequim Laboratory and the Columbus-Based Toxicology Laboratory (ToxNW) as a practicing scientist member. I worked closely with other committee members (a veterinarian, other practicing scientists involved in animal research, scientists not involved in animal research and a community member not affiliated with Battelle) to review all animal-use protocols prior to implementation. We were responsible for oversight of animal care and use as required by law and ensured study design protocols met all criteria prior to issuance of

IACUC approval. In addition, we inspected, monitored, and evaluated ongoing animal care and use and addressed animal welfare concerns.

My responsibilities grew again in November 2011, when I was approved by the National Toxicology Program (NTP) as the Toxicology Discipline Leader for inhalation studies performed at Battelle. In this role, I provided leadership for all of NTP's research and testing efforts in the characterization of toxicological and carcinogenic potential of chemicals, mixtures and agents.

In the fall of 2013, I transitioned from Battelle to Veritox, Inc., a health-based consulting company focusing on toxicology and industrial hygiene. Currently I am a Principal Toxicologist at Veritox, Inc.

My company charges $400 per hour for my time to consult in this matter, and charges $600 per hour for deposition and trial testimony.

My current CV is attached to this report as Attachment 1. My recent testimony list is included as Attachment 2.

C. BASIS OF OPINIONS

The basis for my opinions in this case includes my education; my training in basic science; my experience in toxicology in general and as specifically related to exposure to asbestos, talc, heavy metals and chemicals (including fragrances); my review and analysis of published literature on the effects of asbestos, talc, cobalt, chromium, nickel and fragrance ingredients; and my review of case records.

D. MATERIALS RECEIVED FOR REVIEW

- Discovery Confidentiality Order, 3/1/17 with Exhibit A
- Deposition of Michael Crowley, PhD, 1/4/19
- Deposition of Shawn Levy, PhD, 1/11/19
- Deposition of Laura Plunkett, PhD, DABT, 12/19/18
- Deposition of Dr. Ghassan Saed, 1/23/19
- Deposition of Dr. Ghassan Saed, 2/14/19
- Deposition of Judith Zelikoff, PhD, 1/21/19
- Expert Report of Alan Campion, PhD, 11/16/18 with Exhibits A-C
- Expert Report of Arch Carson, MD, PhD, 11/16/18 with Exhibit A-B
- Expert Report of Daniel L. Clarke-Pearson, MD, 11/16/18 with Exhibits A-C

- Expert Report of Robert B. Cook, PhD, 11/16/18 with Appendix A-B and Exhibits A-B
- Expert Report of Michael M. Crowley, PhD, 11/12/18 with Appendix A-B and CV
- Expert Report of Sarah E. Kane, MD, 11/15/18 with Exhibits A-B
- Expert Report of David A. Kessler, MD, 11/16/18 with Schedules 1-4 and Appendix A-C
- Expert Report of Mark Krekeler, PhD, 11/16/18 with Exhibits A-B
- Expert Report of Shawn Levy, PhD, 11/16/18 with Exhibits A-B
- Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD, 11/14/18
- Expert Report of Anne McTiernan, MD, PhD, 11/16/18 with Tables 1-4 and Exhibit A
- Expert Report of Laura M. Plunkett, PhD, DABT, 11/16/18 with Appendix A-E
- Expert Report of Dr. Ghassan M. Saed, 11/16/18 with Exhibits A-C
- Expert Report of Jack Siemiatycki, MSc, PhD, 11/16/18 with CV
- Expert Report of Sonal Singh, MD, MPH, 11/16/18 with Exhibits A-B
- Expert Report of Ellen Blair Smith, MD, 11/16/18 with Exhibits A-C
- Expert Report of Rebecca Smith-Bindman, MD, 11/15/18 with Exhibits A-C
- Expert Report of Judith Wolf, MD, 11/16/18 with Exhibits A-B
- Expert Report of April Zambelli-Weiner, PhD, MPH, 11/16/18 with Appendix A-D
- Expert Report of Judith Zelikoff, PhD, 11/16/18 with Exhibits A-C
- Expert Report Judith Zelikoff, PhD Report (Highlighted)
- Cook Documents Cited In Report – Johnson & Johnson
- Cook Documents Cited In Report – Imerys
- Krekeler Documents Cited In Report – Johnson & Johnson
- Krekeler Documents Cited In Report – Imerys
- Crowley Documents Cited in Report – Imerys and Johnson & Johnson
- CV of William Edward Longo, PhD and Testimony Listing 2014-2018
- Environmental Chemistry 2 snip
- Dr. Ghassan M. Saed Lab Notebooks [SAED000001-97]
- Formula Declaration Report, 12/3/09 [JNJTALC000149667-68]
- Formula Declaration Report, 10/9/18 [JNJTALC000891091-104]

- Dr. Ghassan M. Saed Manuscript, 1/3/19
- Food and Drug Administration. Response from the FDA to Dr. Epstein regarding Citizen Petitions requesting cosmetic talc products be labeled with a cancer warning. Re Docket No. 94P-0420 and FDA-2008-P-0309-0001/CP; 2014.
- Exhibit 1 [Attorneys' Eyes Only]
- Exhibit 2 [Attorneys' Eyes Only]
- Exhibit 3 [Attorneys' Eyes Only]
- Expert Report of Robert B. Cook, PhD, 1/22/19
- Expert Report of Mark Krekeler, PhD, Addendum, 1/17/19
- Supplemental Report of William E. Longo, PhD, and Mark W. Rigler, PhD, 1/15/19
- Second Supplemental Report of William E. Longo, PhD, and Mark W. Rigler, PhD, 2/1/19
- Lee W. Poye, J3 Resources, Inc., JH18104277 MAS Split of 21 Historic Talc Samples by XRD, 12/12/18 (Sampled: 11/28/18; Received: 12/5/18) with COC
- Lee W. Poye, J3 Resources, Inc., JH18104432 MAS Split of 2 Historic Talc Samples by XRD, 12/20/18 (Shipped: 12/12/18; Received: 12/13/18) with COC

E. BACKGROUND

1. Toxicology

Toxicology is the study of adverse effects of chemical, biological or physical agents on living organisms or ecosystems, including the prevention and amelioration of such adverse effects.[1]

2. Hazard versus risk

Toxicologists evaluate compounds using the terms hazard and risk, which represent two interrelated, but different, concepts. Specifically:

- **Hazard** is an inherent property of a single chemical or mixture to cause adverse effects. Exposure levels are not considered in hazard identification, which (as explained below) is the first step of human health risk assessment.
- **Risk** is the probability that a specified biological effect (hazard) will occur following exposure to a chemical or mixture. Risk incorporates exposure levels or dose. Confusion arises due to the vernacular use of risk (by non-toxicologists) to convey any undesirable event or outcome (e.g., "risk of rain" or "risk of a fall").

[1] Hayes, A.W. Hayes' Principles and Methods of Toxicology. 6th ed. Boca Raton: CRC Press: Taylor & Francis. 2014., p. 597.

Toxicologists use scientific studies and data to determine types of hazard(s) for chemical, biological, or physical agent exposure (e.g., adverse effects such as acute effects, cancer, birth defects, or death) and determine risk of adverse effects through a "Human Health Risk Assessment" process, as discussed in later sections of this report.

Toxicologists do not consider hazard alone in the absence of exposure and/or dose because every agent to which humans may be exposed presents an inherent hazard to health at a sufficiently high dose (e.g., even water can be lethal when ingested in sufficient quantity). Use of a hazard statement alone without incorporation of dose to assess potential risk for human health effects is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

3. Dose-response assessment

The dose-response relationship is the most fundamental and pervasive concept in toxicology. It relies on the fundamental knowledge that each chemical has toxic properties that become apparent as an increasing quantity of that agent is consumed or absorbed. Understanding this relationship is essential to interpreting toxicology concepts, data and recommendations. Dose-response assessment is a way to measure or characterize the relationship between exposure to some amount of an agent and the incidence of an adverse response.[2]

The term "threshold" refers to the level of exposure at which an effect is first observed.[3] It is not true that exposure to "toxic chemicals" at any dose produces adverse effects, although this opinion abounds in the lay public. "The fact that dosage defines toxicity for all chemicals has been recognized for centuries."[4]

Exposure-disease relationships are very important for showing that an exposure caused an effect.[5] Characterizing the dose-response relationship requires knowledge of the intensity of exposure, the concentration over time relationship, and the shape of the dose-response curve. How a body metabolizes a chemical at different doses, the chemical's persistence over time, and an understanding of how a chemical behaves in humans compared to animals are also important aspects of a dose-response evaluation.[6] Adverse responses to any chemical do not necessarily occur from documented exposure or odor detection. The dose of a chemical determines whether that chemical is toxic or nontoxic in a given set of circumstances. Appreciation and application

[2] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019. p. 34.
[3] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019. p. 36; Williams, P.L., James, R.C. and Roberts, S.M. Principles of Toxicology: Environmental and Industrial Applications. 2nd ed. New York: Wiley. 2000.p. 15; Zenz, C., Dickerson, O.B. and Horvath, E.P., Jr. Occupational Medicine. 3rd ed. St. Louis, MO: Mosby Yearbook, Inc. 1994.
[4] Montgomery, M.R. and Reasor, M.J. A toxicologic approach for evaluating cases of sick building syndrome or multiple chemical sensitivity. J Allergy Clin Immunol. 94(2 Pt 2):371-75, 1994.
[5] Bingham, E., Cohrssen, B. and Powell, C.H. Patty's Toxicology. 5th ed. New York: John Wiley. 2001.
[6] Hayes, A.W. Hayes' Principles and Methods of Toxicology. 6th ed. Boca Raton: CRC Press: Taylor & Francis. 2014.

of this basic tenet of toxicology, the dose-response relationship, are necessary when objectively evaluating chemically mediated effects.[7]

All chemicals have a dose below which the probability of a response is zero. This important toxicological concept has long been recognized and is well defined.[8]

4. Human health risk assessment

Human health risk assessment is a process by which data on the metabolism and toxicity of a chemical/agent are used to estimate the potential hazard(s) to humans at specific doses. The process often involves extrapolating data from laboratory animals to humans. Risk assessment results are used by regulatory agencies to define acceptable levels of exposure of human populations to chemicals/agents with intrinsic hazards.

The human health risk assessment process was originally described as an activity characterized by four general stages by the National Research Council in 1983. These four steps, which remain current in modern risk assessment activities, are:

1. **Hazard identification**: the process of determining whether an agent can cause an adverse health effect in humans. It frequently relies on whether the agent can cause adverse effects in laboratory animals.
2. **Dose-response assessment**: the process of determining how adverse effects are related to dose. It generally requires extrapolation from high to low doses and extrapolation from animals to humans.
3. **Exposure assessment**: the process of estimating human exposure to the agent. It takes into account exposure routes (ingestion, inhalation, dermal), levels (concentrations) and durations.
4. **Risk characterization**: the process of estimating the incidence of a health effect under the various conditions of human exposure described in exposure assessment. It combines exposure and dose-response assessments and describes the uncertainties of those evaluations. It is an estimate of the magnitude of the public health problem.[9]

Toxicologists utilize the four steps above to analyze and assess potential risk to human health associated with specific levels of exposure. Use of hazard identification statements alone, without knowledge, analysis and assessment of exposure levels associated with adverse effects with those estimated for the population, is not consistent with the previously outlined generally accepted methods used by toxicologists to assess potential risk to human health. Toxicologists do not consider hazard alone in the absence of exposure and/or dose because every agent to which

[7] Montgomery, M.R. and Reasor, M.J. A toxicologic approach for evaluating cases of sick building syndrome or multiple chemical sensitivity. J Allergy Clin Immunol. 94(2 Pt 2):371-75, 1994.
[8] Hayes, A.W. Hayes' Principles and Methods of Toxicology. 6th ed. Boca Raton: CRC Press: Taylor & Francis. 2014; Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019.
[9] National Research Council. Risk Assessment in the Federal Government – Managing the Process. Washington DC: National Academy Press. 1983.

humans may be exposed presents an inherent hazard to health at a sufficiently high dose (e.g., even water can be lethal when ingested in sufficient quantity).

Application of toxicological risk assessment data can result in derivation of conservative estimates for exposure concentrations to which a person can be exposed over a lifetime without an adverse health impact.[10] These human health toxicity values include:

- **Minimal Risk Levels (MRLs):** MRLs represent an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. They are derived by the Agency for Toxic Substances and Disease Registry (ATSDR), a public health agency in the U.S. Department of Health and Human Services.[11]
- **Permissible Daily Exposure (PDE):** PDEs represent the daily exposure level considered to be protective of public health for all patient populations.[12] They are derived by the US FDA,[13] the ICH[14] and the United States Pharmacopoeia Convention (USP).[15]
- **Tolerable Daily Intake (TDI):** TDIs represent the daily exposure level considered to be protective of public health. They are derived by the European Food Safety Authority (EFSA).

Human health toxicity values (e.g., MRLs and PDEs) are calculated by selecting, based on the current scientific dataset, the most sensitive (lowest) concentration that did not cause an effect in animals and then dividing by uncertainty and modifying factors to reflect the uncertainty in extrapolation of the current animal dataset to effects that may occur in humans.[16]

5. The International Agency for Research on Cancer (IARC)

The International Agency for Research on Cancer (IARC) is part of the World Health Organization that promotes international collaboration in cancer research.[17] IARC selects chemicals/agents to evaluate based on evidence of human exposure and some evidence or suspicion of carcinogenicity and prepares agent-specific "Monographs."

[10] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 139-40.
[11] ATSDR. Minimal Risk Levels (MRLs) for Hazardous Substances. Last updated 08/02/2018. Available from: https://www.atsdr.cdc.gov/mrls/mrllist.asp. Accessed: 01/15/2019.
[12] ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014.
[13] US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015.
[14] ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014.
[15] Pharmacopeia, U.S. Chapter 232: Elemental Impurities-Limits. In: US Pharmacopeia 39 The National Formulary 34. Rockville, MD: U.S. Pharmacopoeia Convention; 2016.
[16] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 139-40.
[17] IARC. IARC's Mission: Cancer research for cancer prevention. https://www.iarc.fr/about-iarc-mission. Accessed: January 14, 2019.

a. IARC identifies potential hazards—it does not perform human health risk assessments

IARC Monographs evaluate cancer hazard. They do not evaluate human risk (i.e., they evaluate whether an agent is capable of causing cancer under any circumstances; they do not estimate carcinogenic effects expected from exposure to a cancer hazard). The *Preamble for the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* specifies:

> *"The **Monographs are an exercise in evaluating cancer hazards**, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher* [emphasis added]".[18]

The general process for IARC Monograph generation is also outlined in the *Preamble*. In general:

- Participants for the Expert Working Group are selected by IARC staff (in consultation with other experts).
- IARC collects relevant biological and epidemiological data from recognized sources of information on carcinogenesis; some meeting participants prepare preliminary working papers for specific sections and supplement IARC literature with their own searches.
- The Working Group reviews obtained materials and prepares preliminary working papers.
- The Working Group meets for 7 to 8 days to discuss and finalize texts. All exposure data, studies regarding cancer in humans, studies evaluating cancer in animals and any other relevant data, such as mechanistic information, is reviewed.
- The assembled data are compared to and assigned into predefined IARC evidence categories for human and animal carcinogenicity (described in Table 1), and the data are reviewed for mechanistic support for human disease.
- Finally, the body of evidence is considered as a whole for an overall evaluation and conclusion of the carcinogenicity of the agent to humans.
- The overall carcinogenicity category to humans is assigned based on the general matrix given in Table 2.

Notably, IARC evidence categories for animal carcinogenicity described in Table 1 only consider positive evidence of carcinogenicity and do not take into account how many studies failed to observe a carcinogenic response.

[18] IARC. Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France. 2006.

Table 1. IARC Classification categories for evidence of human and animal carcinogenicity

Human classification	**Classification criteria**[19]
Sufficient evidence of carcinogenicity	Positive association observed, for which chance, bias and confounding could be ruled out with reasonable confidence
Limited evidence of carcinogenicity	Positive association observed, but chance, bias and confounding could NOT be ruled out with reasonable confidence
Inadequate evidence of carcinogenicity	Studies are insufficient or non-existent
Evidence suggesting lack of carcinogenicity	Several consistent studies covering full range of exposure levels that humans are known to encounter show no positive association between exposure to the agent and any studied cancer at any observed level of exposure; bias and confounding should be ruled out with reasonable confidence

Animal classification	**Classification criteria**
Sufficient evidence of carcinogenicity	Increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms in: (a) 2 or more species or (b) 1 species if from 2 or more independent studies (sometimes 2 sexes in well-conducted study)
Limited evidence of carcinogenicity	Evidence is limited for neoplasms because: (a) evidence stems from a single experiment (b) unresolved questions regarding (design, conduct, interpretation of studies) (c) benign neoplasms / lesions of uncertain neoplastic potential (d) promoting activity in a narrow range of tissues or organs
Inadequate evidence of carcinogenicity	No data or major qualitative / quantitative study limitations
Evidence suggesting lack of carcinogenicity	2 or more species showing non-carcinogenicity; conclusion limited to species, age, tumor site, levels of exposure and study conditions

[19] IARC. Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France. 2006.

Table 2. IARC Classification categories for human carcinogenicity

Rating	Description[20]
Group 1 [Carcinogenic]	Agent is carcinogenic to humans. Classified with: (a) Sufficient evidence in humans, or (b) Exceptionally: Sufficient evidence in animals; and Less than sufficient evidence in humans; and Strong evidence that carcinogenicity mechanism is relevant for humans
Group 2A [Probably carcinogenic]	Agent is probably carcinogenic to humans. Classified with: (a) Limited evidence in humans, and Sufficient evidence in animals; or (b) Inadequate evidence in humans, and Sufficient evidence in animals; and Strong evidence that carcinogenicity mechanism is relevant for humans; or (c) Exceptionally: Limited evidence in humans, and Agent belongs, based on mechanistic considerations, to a class of agents previously classified in Group 1 or Group 2A
Group 2B [Possibly carcinogenic]	Agent is possibly carcinogenic to humans. Classified with: (a) Limited evidence in humans, and Less than sufficient evidence in animals; or (b) Inadequate evidence in humans, and Sufficient evidence in animals; or (c) Inadequate evidence in humans, Less than sufficient evidence in animals, and Supporting evidence from mechanistic and other relevant data
Group 3 [Not classifiable]	Agent is not classifiable as to its carcinogenicity to humans. Classified with: (a) Inadequate evidence in humans, and Inadequate or limited evidence in animals; or (b) Exceptionally: Inadequate evidence in humans, and Sufficient evidence in animals; and Strong evidence that animal carcinogenicity mechanism does not operate in humans; or (c) The agent does not fall into any other group
Group 4 [Probably not carcinogenic]	Agent is probably not carcinogenic to humans. Classified with: (a) Evidence suggesting lack of carcinogenicity in humans, and Evidence suggesting lack of carcinogenicity in animals; or (b) Inadequate evidence of carcinogenicity in humans, and Evidence suggesting lack of carcinogenicity in animals, and Strongly supported by a broad range of mechanistic and relevant data

[20] IARC. Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France. 2006.

b. IARC conclusions

IARC does not randomly select agents for evaluation; rather, it makes the selection based on: (1) pre-existing evidence of human exposure and (2) some evidence or suspicion of carcinogenicity.[21] Thus, all agents evaluated by IARC were evaluated because they were considered possible carcinogens. As of November 9, 2018, IARC had concluded that 1 out of 1,013 evaluated agents was probably not carcinogenic to humans (classifications summarized in Table 3). Classification for perineal use of talc-based body powder as possibly carcinogenic (Group 2B), simply corresponded with a failure of the Working Group to rule out bias and confounding as causative for the observed epidemiology results and the limited animal carcinogenicity data (IARC's conclusion for talc not containing asbestos or asbestiform fibers was: *limited* evidence in humans and *limited* evidence in animals).[22] Other agents classified as Group 2B (possibly) carcinogenic include the whole leaf extract of aloe vera, cobalt and cobalt compounds, and occupational exposure as a firefighter.[23]

Table 3. Agents Classified by IARC Monographs

Group	Classification	Number of agents[24]	Percent of Monographs
Group 1	Carcinogenic to humans	120	11.8%
Group 2A	Probably carcinogenic to humans	82	8.1%
Group 2B	Possibly carcinogenic to humans	311	30.7 %
Group 3	Not classifiable as to its carcinogenicity to humans	499	49.3 %
Group 4	Probably not carcinogenic to humans	1	0.1%

6. Association vs. causation: The Bradford Hill criteria

The first consideration advanced by Sir Austin Bradford Hill for judging association vs. causation was "strength of association." An association is any observed relationship (correlation) between an exposure and an effect. Observing an association between an exposure and an outcome alone is not sufficient to establish that the event caused the outcome (causality). The strength, or magnitude, of a potential exposure-associated effect is commonly expressed as a ratio between the observed frequency of the effect in the exposed groups and non-exposed groups studied. This measurement, derived from human epidemiology studies, is commonly expressed as a "relative risk" (RR) or an "odds ratio" (OR).

[21] IARC. Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France. 2006.
[22] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.
[23] IARC. Agents classified by the IARC Monographs, volumes 1-123. Last updated Nov. 9, 2018. Available from: https://monographs.iarc.fr/wp-content/uploads/2018/09/List_of_Classifications.pdf. Accessed: January 21, 2019.
[24] IARC. Agents classified by the IARC Monographs, volumes 1-123. Last updated Nov. 9, 2018. Available from: https://monographs.iarc.fr/agents-classified-by-the-iarc/. Accessed: January 13, 2019.

- An association between an exposure and an effect is suspected when the resulting RR is increased (above 1) as long as the corresponding 95% confidence interval (CI) does not include 1, because a RR of 1 indicates exposure did not affect disease incidence.

  CIs represent the range in which, based on the observed data, the true value is expected to fall. They are computed using the experimentally observed data and represent the range of results expected if samples from new studies were repeatedly drawn from the same population.[25]

Different study designs are commonly used to study associations between disease and exposure in human populations:

- **Cohort studies** select studied groups based on exposure: groups of exposed and non-exposed individuals are followed over time to see who gets the disease
- **Case-control studies** select cases (people with the disease) and select appropriate controls (people without the disease) and ask them (or their beneficiaries) to recall information regarding exposure.

Cohort studies are considered to be stronger evidence for associations than case-control studies because they are less susceptible to selection bias and informational bias. Selection bias comes from the method used to choose study participants. Informational biases include recall bias and interviewer bias. "…*recall bias may occur because patients with chronic diseases (or their relatives) may ponder the possible causes of their disease, and, therefore, they may be more likely to recall some past exposures than would healthy controls*."[26]

Simple observation of an association is not sufficient to establish causation. Instead, once an association is observed, all available data are considered to assess whether the association reflects a true cause and effect relationship using the Bradford Hill criteria.[27] These criteria (or series of considerations), published in 1965, provide guidance regarding when an observed association between an exposure and a particular outcome or disease could be elevated to an interpretation of causation.[28] At the time, the considerations were largely aimed at evaluating relationships with epidemiological and occupational data; however, a similar framework (given in Table 4) is applied by toxicologists to evaluate experimental and observational chemical

[26] Checkoway, H., Pearce, N. and Kriebel, D. Research Methods in Occupational Epidemiology. 2nd ed. Kelsey, J.L., Marmot, M.G., Stolley, P.D., Hofman, A., editors. New York, NY: Oxford University Press. 2004., p. 196-97.
[27] Federal Judicial Center and National Research Council. Reference Manual on Scientific Evidence. 3rd ed. Washington, D.C.: National Academies Press. 2011.
[28] Hill, A.B. The environment and disease: association or causation? Proc Royal Soc Med. 58:295-300, 1965.

toxicity data[29] and is very similar to those outlined for appropriate causal inferences in the *Reference Manual on Scientific Evidence*.[30]

Confidence that a potential causal relationship exists between an exposure and an effect increases with the strength of the association observed in a well-designed study. The magnitude of this potential relationship is described by the observed RR (or OR). Magnitude is important because higher estimates of RR are more likely to remain if all bias and confounding (which are present to some extent in all studies) could be eliminated.[31] Epidemiologists regard RR and OR values of 2.0 or less as "weak" or "small" and suggest that any value less than 3.0 be considered "tentative."[32] A more recent publication indicated that an RR of 2.0 or more merits consideration when it is from a cohort study because cohort designs are less susceptible to bias than case-control studies, which should be discounted when values are less than 3.0.[33]

Because Hill did not advocate the use of the criteria to provide "hard-and-fast rules of evidence," they have evolved to establishing a "weight of evidence" to support the likelihood that a chemical exposure causes a particular health outcome.[34] In this process, each criterion is evaluated for its strength of support and an overall conclusion is based upon whether all the evidence taken from a number of sources supports a judgment of causality.[35]

[29] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 42-43.
[30] Federal Judicial Center and National Research Council. Reference Manual on Scientific Evidence. 3rd ed. Washington, D.C.: National Academies Press. 2011., p. 599-600.
[31] Grimes, D.A. and Schulz, K.F. False alarms and pseudo-epidemics: the limitations of observational epidemiology. Obstet Gynecol. 120(4):920-7, 2012; Shapiro, S. Causation, bias and confounding: a hitchhiker's guide to the epidemiological galaxy. Part 2. Principles of causality in epidemiological research: confounding, effect modification and strength of association. The journal of family planning and reproductive health care. 34(3):185-90, 2008.
[32] Shapiro, S. Causation, bias and confounding: a hitchhiker's guide to the epidemiological galaxy. Part 2. Principles of causality in epidemiological research: confounding, effect modification and strength of association. The journal of family planning and reproductive health care. 34(3):185-90, 2008.
[33] Grimes, D.A. and Schulz, K.F. False alarms and pseudo-epidemics: the limitations of observational epidemiology. Obstet Gynecol. 120(4):920-7, 2012.
[34] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019. p. 43.
[35] Elwood, J.M. The diagnosis of causation. Ch. 8 In: Causal Relationships in Medicine A Practical System for Critical Appraisal. Elwood, J.M., editor. New York: Oxford University Press; 1988. p. 163-82.

Table 4. Causation in Toxicology: Bradford Hill Criteria (as adapted by *Casarett and Doull's Toxicology*, 2019)

Criteria
1. Strength of association. Hill suggested that strong associations support a causal relationship (for example, a 10x increase in death rate could serve as strong evidence in favor of a potential relationship). Hill was careful not to dismiss modest changes.
2. Consistency of findings. Hill recommended results be replicated in different studies, and advocated using different experimental approaches that could reach similar conclusions.
3. Specificity of association. Likelihood of a cause and effect relationship is strengthened by how tightly linked an outcome is to the exposure.
4. Temporal sequence. Cause must occur before the effect.
5. Biological gradient. Establishment of a clear dose-response relationship such that greater exposure is linked to a more severe outcome provides further causation support.
6. Biological or theoretical plausibility. The ability to postulate a reasonable mechanism of action can strengthen the likelihood of causation. This does not, however, address the potential that the current state of knowledge is limited.
7. Coherence with established knowledge. The association between the cause and effect should reasonably align with the current understanding of disease pathogenesis.
Other criteria: 1. Support from a decreased incidence of disease following an intervention to limit exposure. 2. The ability to draw analogies between related chemicals can lessen the depth of experimental validation.

F. COSMETIC TALC PRODUCTS

1. Key opinion

- Scientific literature does not support a causal relationship between perineal talc use and ovarian cancer.

2. Overview

Scientific analysis, using the Bradford Hill Criteria, does not support a causal relationship between cosmetic talc use and ovarian cancer. Key points (reviewed in the sections that follow) include:

1. On balance, scientific literature provides no support for a potential relationship between perineal cosmetic talc use and ovarian cancer.
   - Case-control epidemiology studies sometimes show a small, statistically significant association between talc use and disease, but they contain unresolved confounding, and cohort studies fail to replicate their observations.
   - Dose-response relationships are unclear.
2. Animal toxicology studies do not observe increased ovarian cancers, either (1) following direct implantation of talc onto ovaries or (2) following a lifetime of body dusting and inhalation exposures.

3. Scientific evidence does not show talc deposited on the perineum migrates to the ovaries. IARC agrees, and concluded that the scientific evidence for retrograde transport of talc to the ovaries in normal women was weak and that studies in animals (including rodents and non-human primates) showed no evidence of retrograde transport of talc to the ovaries.[36]

4. Biological plausibility for carcinogenicity has not been shown.

   – Propensity of agents to induce inflammation (at any dose) does not establish biological plausibility for talc and ovarian cancer.

Other published scientific expert groups and peer-reviewed literature agree that the current scientific data do not support an association and/or a causal relationship between talc use and ovarian cancer. This includes:

- **National Cancer Institute** (2019): "*weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer*."[37]

- **Craig & Ziv-Gal** (2018): "*some studies suggest a potential link between ovarian cancer and talc exposure in both epidemiological and experimental models. However, more studies are needed to confirm these findings and to better understand the levels, timing of exposure, and genetic backgrounds that may be associated with a greater risk*."[38]

- **Cosmetic Ingredient Review Expert Panel** (2015) assessed the safety of talc and determined that studies do not support a causal link between the cosmetic use of talc in the perineal area and ovarian cancer.[39]

- **IARC** (2010): "*Perineal use of talc-based body powder is possibly carcinogenic to humans (Group 2B).*" As discussed above (see section E.5, page 10), the role of IARC is to identify potential hazards. Its classification of talc-based body powder in Group 2B is associated with a failure to rule out bias and confounding as causative for the observed epidemiology results.[40] Thus, with its categorization as Group 2B,[41] IARC agreed that the scientific evidence is not sufficient for a causal relationship. If it had deemed the scientific dataset supported a causal relationship, its assessment would have resulted in a

[36] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.
[37] NCI. Ovarian, fallopian tube, and primary peritoneal cancer prevention (PDQ) - Health professional version. Bethesda, MD: National Cancer Institute; Last updated 1/4/19. Available from: https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq.
[38] Craig, Z.R. and Ziv-Gal, A. Pretty Good or Pretty Bad? The Ovary and Chemicals in Personal Care Products. Toxicol Sci. 162(2):349-60, 2018.
[39] Fiume, M.M., Boyer, I., Bergfeld, W.F., *et al.* Safety assessment of talc as used in cosmetics. International Journal of Toxicology. 34 (Supplement I):66S-129S, 2015; Bergfeld, W.F., Belsito, D.V., Hill, R.A., *et al.* Safety assessment of talc as used in cosmetics. Final report. Washington, D.C. Cosmetic Ingredient Review, April 12, 2013.
[40] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010; Munn, L.L. Cancer and inflammation. Wiley interdisciplinary reviews Systems biology and medicine. 9(2), 2017.
[41] Langseth, H., Hankinson, S.E., Siemiatycki, J. and Weiderpass, E. Perineal use of talc and risk of ovarian cancer. J Epidemiol Community Health. 62(4):358-60, 2008; IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.

Group 1 carcinogen designation. The literature published after the IARC monograph is consistent with IARC's findings, i.e., does not support Group 1 designation.

3. Talc minerology and uses

Talc has complex minerology. While talc is well-defined as a mineral, the ore bodies from which it is mined and the commercial products sold as talc are highly variable.[42] Commercial talc may contain essentially 100% of the mineral talc or may contain relatively little, depending upon the grade and source.[43] Geologic literature indicates that talc deposits can range from essentially pure talc to deposits that contain varying amounts of accessory minerals, including chlorite, dolomite, magnesite, mica, quartz, serpentines and amphiboles. Even within a single talc deposit, the amount of non-talc minerals can be highly variable across the deposit.[44]

Many minerals, including talc, serpentines and amphiboles, can form in more than one crystalline structure, or "habit," depending upon the geologic conditions under which they formed. Examples of crystal habits are acicular (needle-like), bladed, fibrous, massive, platy and prismatic. Talc typically occurs in massive, platy or fibrous habits.[45] Only pure, platy talc is desirable for cosmetic uses.

Cosmetic grade talc, as its name implies, is a specific grade of talc used for cosmetics, body dusting powders and baby powders.[46] Cosmetic grade talc may also be used medically for talc pleurodesis. In 1990, only 5% of talc produced was used in cosmetics.[47] Other uses of talc include ceramics, insecticides, paint, paper, plastics, refractories, roofing, asphalt filler, crayons and rubber, but industrial grade talc is used in these applications, not cosmetic talc.[48]

Johnson's Baby Powder and Shower to Shower have not been shown to contain asbestos fibers. The absence of asbestos in cosmetic talc is supported by the lack of asbestos-related disease (i.e., mesothelioma) in heavily exposed cosmetic talc miners and in patients who have undergone pleurodesis (direct injection of a talc slurry into the lung's pleural space).[49] The

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[42] Zazenski, R., Ashton, W.H., Briggs, D., *et al.* Talc: occurrence, characterization, and consumer applications. Regul Toxicol Pharmacol. 21(2):218-29, 1995.
[43] Drechsel, D.A., Barlow, C.A., Bare, J.L., Jacobs, N.F. and Henshaw, J.L. Historical evolution of regulatory standards for occupational and consumer exposures to industrial talc. Regul Toxicol Pharmacol. 92:251-67, 2018.
[44] Van Gosen, B.S., Lowers, H.A., Sutley, S.J. and Gent, C.A. Using the geologic setting of talc deposits as an indicator of amphibole asbestos content. Presented at: Environmental Geology; 2004: Springer-Verlag; 2004. p. 920-39.
[45] Deer, W.A., Howie, R.A. and Zussman, J. An Introduction to the Rock Forming Minerals. London: Longman Group Limited. 1966. p. 228.
[46] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010; Virta, R.L. The talc industry – an overview. Washington, D.C. Report No.: Information Circular 9220. 1989.
[47] US EPA. Health Assessment Document for Talc. Research Triangle Park, NC. Report No.: EPA 600/8-91/217. March, 1992.
[48] Chidester, A.H., Engel, A.E.J. and Wright, L.A. Talc resources of the United States. Washington, D.C. Report No.: 1167. 1964; Virta, R.L. The talc industry – an overview. Washington, D.C. Report No.: Information Circular 9220. 1989.
[49] Coggiola, M., Bosio, D., Pira, E., *et al.* An update of a mortality study of talc miners and millers in Italy. Am J Ind Med. 44(1):63-69, 2003; Lange, P., Mortensen, J. and Groth, S. Lung function 22-35 years after treatment of

following is an evaluation of the current scientific knowledge of the relationship between cosmetic talc exposure and ovarian cancer.

4. Human epidemiology studies of talc and ovarian cancer

Many peer-reviewed, published epidemiology studies have evaluated the relationship between perineal talc use and ovarian cancer.

a. Case-control studies

Most of these studies employed a case-control study design, and Table 5 provides a summary of the individual investigations of case-control studies. Results, given in terms of the odds ratio (OR, derived in case-control studies as an approximation of relative risk [RR]) reported in each study, indicated:

- No statistically significant effect was observed with perineal talc use in about half of the studies reviewed.
- Many studies failed to assess any metric of exposure, simply assessing perineal talc use as "ever exposed" vs. "never exposed."
- All statistically significant increases in risk were ≤ 1.6, which is considered a "weak" association within the scientific community, for which bias and confounding cannot be eliminated as causal factors (instead of the agent of interest; see page 14).
  - Notably, many studies with statistically significant findings stemmed from the same geographical area (7 from New England), indicating a potential bias if an unidentified confounding factor made women more likely to use talc and to develop ovarian cancer.
  - At least 2 of the studies that observed a positive association were based on the same group of women (the second study expanded the number of participants)[50] or consisted of or included compilations of other, separately reported case-control studies.[51]

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idiopathic spontaneous pneumothorax with talc poudrage or simple drainage. Thorax. 43(7):559-61, 1988; Pierce, J.S., Riordan, A.S., Miller, E.W., Gaffney, S.H. and Hollins, D.M. Evaluation of the presence of asbestos in cosmetic talcum products. Inhal Toxicol. 29(10):443-56, 2017; Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit. A survey of the long-term effects of talc and kaolin pleurodesis. Br J Dis Chest. 73(3):285-88, 1979; Viskum, K., Lange, P. and Mortensen, J. Long term sequelae after talc pleurodesis for spontaneous pneumothorax. Pneumologie. 43(2):105-06, 1989; Wild, P., Leodolter, K., Refregier, M., *et al.* A cohort mortality and nested case-control study of French and Austrian talc workers. Occup Environ Med. 59(2):98-105, 2002; Wergeland, E., Andersen, A. and Bærheim, A. Morbidity and mortality in talc-exposed workers. Environ Health Perspect. 17:505-13, 1990.

[50] Wu, A.H., Pearce, C.L., Tseng, C.C. and Pike, M.C. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 24(7):1094-100, 2015; Wu, A.H., Pearce, C.L., Tseng, C.C., Templeman, C. and Pike, M.C. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer. 124(6):1409-15, 2009.

[51] Cramer, D.W., Welch, W.R., Scully, R.E. and Wojciechowski, C.A. Ovarian cancer and talc: a case-control study. Cancer. 50(2):372-76, 1982; Harlow, B.L., Cramer, D.W., Bell, D.A. and Welch, W.R. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol. 80(1):19-26, 1992; Cramer, D.W. and Xu, H. Epidemiologic evidence for

- A recent meta-analysis review that combined results from 24 case-control studies observed that any talc use was associated with a slightly increased OR of 1.35 (95% CI=1.24-1.39).[52] However, the results of the meta-analysis are of unknown accuracy given that the methods used to select studies for inclusion were flawed. The combined dataset included case-control studies by Purdie et al. (1995)[53] and Green et al. (1997),[54] which had evaluated the same 860 ovarian cases from Australia (as specified by Green et al., 1997) and observed statistically significantly increased OR for ovarian cancer with perineal talc use. The impact of duplicating this data in the meta-analysis is unknown and results in an unreliable study outcome.

b. Cohort studies

Cohort studies are considered to be stronger evidence for associations than case-control studies. Cohort studies for risk of ovarian cancer with talc exposure include three cohorts:

- The Nurses' Health Study enrolled 121,700 women in 1976 and initially followed them to 1996. A second study expanded the follow-up through June 2006. No association between perineal talc use and ovarian cancer was observed during the first (RR=1.09, 95% CI=0.86-1.37)[55] or second (1.06, 95% CI=0.89-1.28)[56] follow-up periods.

- The Women's Health Initiative enrolled 61,576 women from 1993-1998 and followed them to 2012. No association between perineal talc use and ovarian cancer was observed (RR=1.06, 95% CI=0.87-1.28).[57]

- The Sister Study enrolled 41,654 women who had a sister diagnosed with breast cancer from 2003-2009. Over the follow-up period (6.6 yr median), no association between perineal talc use and ovarian cancer was observed (RR=0.73, 95% CI=0.44-1.2).[58]

When risk was separated by ovarian cancer subtype, the first follow-up period for the Nurses' Health Study observed a statistically significant elevation in risk of invasive serous

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uterine growth factors in the pathogenesis of ovarian cancer. Ann Epidemiol. 5(4):310-14, 1995; Cramer, D.W., Liberman, R.F., Titus-Ernstoff, L., *et al.* Genital talc exposure and risk of ovarian cancer. Int J Cancer. 81(3):351-6, 1999; Cramer, D.W., Titus-Ernstoff, L., McKolanis, J.R., *et al.* Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-31, 2005; Gates, M.A., Tworoger, S.S., Terry, K.L., *et al.* Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 17(9):2436-44, 2008.

[52] Penninkilampi, R. and Eslick, G.D. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. Epidemiology Epidemiology. 29(1):41-49, 2018.

[53] Purdie, D., Green, A., Bain, C., *et al.* Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int J Cancer. 62(6):678-84, 1995.

[54] Green, A., Purdie, D., Bain, C., *et al.* Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int J Cancer. 71(6):948-51, 1997.

[55] Gertig, D.M., Hunter, D.J., Cramer, D.W., *et al.* Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 92(3):249-52, 2000.

[56] Gates, M.A., Rosner, B.A., Hecht, J.L. and Tworoger, S.S. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 171(1):45-53, 2010.

[57] Houghton, S.C., Reeves, K.W., Hankinson, S.E., *et al.* Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst. 106(9), 2014.

[58] Gonzalez, N.L., O'Brien, K.M., D'Aloisio, A.A., Sandler, D.P. and Weinberg, C.R. Douching, Talc Use, and Risk of Ovarian Cancer. Epidemiology. 27(6):797-802, 2016.

ovarian cancer with ever talc use (RR=1.4, 95% CI=1.02-1.91).[59] However, this effect was no longer statistically significant when the follow-up was expanded through June 2006 (RR=1.06, 95% CI=0.84-1.35);[60] it was not observed in the Women's Health Initiative Cohort[61] and not evaluated in the Sister Study.[62]

Table 5. Case Control Studies of Ovarian Cancer and Talc Use

Citation[a]	Population (enrollment)	No. Cases / Controls[b]	Exposure category[c]	OR (95 %CI)	Signifi-cant	Dose-response[d]
Cramer, 1982	[New England], Greater Boston (1978-1981)	215 / 215 (H)	Ever / Never	1.61 (1.04-2.49)[e]	+	-
Harlow, 1992	[New England], Boston area (1984-1987)	235 / 239 (H)	Ever / Never	1.5 (1.0-2.1)	+	Borderline
Cramer, 1995	[New England], Greater Boston (1978-1981; 1984-1987)	450 / 454 (H)	Ever / Never	1.6 (1.2-2.1)	+	-
Cramer, 1999	[New England], Eastern MA, New Hampshire (1992-1997)	563 / 523 (P)	Ever / Never	1.60 (1.18-2.15)	+	No
Cramer, 2005	[New England], Eastern MA, New Hampshire (1998-2003)	668 / 721 (P)	Ever / Never	1.16 (0.90-1.49)	–	-
Gates, 2008	[New England], Eastern MA, New Hampshire (1992-2003; 1976-2004)	1385 /1802 (P)	Ever / Never	1.36 (1.14-1.63)	+	Borderline
Cramer, 2016	[New England], Eastern MA, New Hampshire (1992-2008)	2041 / 2100 (P)	Ever / Never	1.33 (1.16-1.52)	+	Yes
Hartge, 1983	Washington DC (1974-1977)	135 /171 (H)	Ever / Never (genital use)	2.5 (0.7-10)	–	-

[59] Gertig, D.M., Hunter, D.J., Cramer, D.W., *et al.* Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 92(3):249-52, 2000.
[60] Gates, M.A., Rosner, B.A., Hecht, J.L. and Tworoger, S.S. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 171(1):45-53, 2010.
[61] Houghton, S.C., Reeves, K.W., Hankinson, S.E., *et al.* Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst. 106(9), 2014.
[62] Gonzalez, N.L., O'Brien, K.M., D'Aloisio, A.A., Sandler, D.P. and Weinberg, C.R. Douching, Talc Use, and Risk of Ovarian Cancer. Epidemiology. 27(6):797-802, 2016.

Table 5. Case Control Studies of Ovarian Cancer and Talc Use

Citation[a]	Population (enrollment)	No. Cases / Controls[b]	Exposure category[c]	OR (95 %CI)	Signifi-cant	Dose-response[d]
Hartge, 1994	Washington DC (1978-1981)	296 / 343 (H)	Occupational, <5 up to ≥10 yr	≥10 yr: 0.5 (0.2-1.5)	–	No
Rosenblatt, 1992	Baltimore, MD (1981-1985)	77 / 46 (H)	Ever / Never (bath)	1.7 (0.7-3.9)	–	No
Wong, 1999	Buffalo, NY area (1982-1995)	462 / 693 (H)	Ever / Never	0.92 (0.24-3.62)[e]	–	No
Kurta, 2012	Western PA, Eastern OH, Western NY (2003-2008)	902 / 1802 (P)	Ever / Never	1.40 (1.16-1.69)	+	-
Ness, 2000	Delaware Valley (1994-1998)	767 /1367 (H)	Ever / Never (genital/rectal)	1.5 (1.1-2.0)	+	No
Moorman, 2009	North Carolina (1999-2008)	Whites: 943 / 868 (P) African Americans: 143 / 189 (P)	Ever / Never Ever / Never	1.04 (0.82-1.33) 1.19 (0.68-2.09)	– –	– –
Whittemore, 1988	California, Northern (1983-1985)	188 / 280 (H)	Ever / Never	1.45 (0.81-2.6)	–	No
Wu, 2015	California, LA County (1992-2008)	1701 / 2391 (P)	Yes / ≤1 yr	1.46 (1.27-1.69)	+	Yes
Wu, 2009	California, LA County (1998-2002)	609 / 688 (P)	Ever / Never (perineal)	1.53 (1.13-2.09)	+	Yes
Mills, 2004	California, Central (2000-2001)	256 / 1122 (P)	Ever / Never	1.37 (1.02-1.85)	+	No
Harlow, 1989	Washington State (1980-1985)	116 / 158 (P)	Ever / Never	1.1 (0.7-2.1)	–	–
Cook, 1997	Washington State (1986-1988)	313 / 422 (P)	Ever / Never	1.6 (0.9-2.8)	–	No
Rosenblatt, 2011	Washington State (2002-2005)	812 / 1313 (P)	Ever /Never (bath)	1.27 (0.97-1.66)	–	No
Schildkraut, 2016	US: African American Cancer Study (2010-2015)	584 / 745 (P)	Ever /Never	1.44 (1.11-1.86)	+	Yes
Tzonou, 1993	Athens, Greece (1989-1991)	189 / 200 (H)	Ever / Never	1.05 (0.28-3.98)	–	–
Booth, 1989	London and Oxford (1978-1983)	235 / 451 (H)	Daily	1.3 (0.8-1.9)	–	No
Chang, 1997	S. Ontario, Canada (1989-1992)	450 / 564 (P)	Any regular talc use	1.42 (1.08-1.86)	+	No
Godard, 1998	Montreal, Canada (1995-1996)	153 /152 (P)	Ever / Never	2.49 (0.94-6.58)	–	–

Table 5. Case Control Studies of Ovarian Cancer and Talc Use

Citation[a]	Population (enrollment)	No. Cases / Controls[b]	Exposure category[c]	OR (95 %CI)	Signifi-cant	Dose-response[d]
Purdie, 1995	Australia (1990-1993)	824 / 860 (P)	Ever / Never	1.27 (1.04-1.54)	+	–
Jordan, 2007	Australia, primarily Queensland (2002-2005)	362 / 751 (P)	Ever / Never	1.10 (0.84-1.45)	–	No
Merritt, 2008	Australia (2002-2005)	1576 / 1509 (P)	Ever / Never	1.17 (1.01-1.36)	+	Borderline
Chen, 1992	Beijing metropolitan area, China (1984-1986)	112 / 224 (P)	Ever / Never	3.9 (0.9-10.6)	–	–
			Occupational	0.9 (0.3-2.9)	–	–

[a] Chen, Y., Wu, P.C., Lang, J.H., *et al.* Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol. 21(1):23-29, 1992; Hartge, P., Hoover, R., Lesher, L.P. and McGowan, L. Talc and ovarian cancer. JAMA. 250(14):1844, 1983; Hartge, P. and Stewart, P. Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981. J Occup Med. 36(8):924-27, 1994; Rosenblatt, K.A., Szklo, M. and Rosenshein, N.B. Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol. 45(1):20-25, 1992; Rosenblatt, K.A., Weiss, N.S., Cushing-Haugen, K.L., Wicklund, K.G. and Rossing, M.A. Genital powder exposure and the risk of epithelial ovarian cancer. Cancer Causes Control. 22(5):737-42, 2011; Cramer, D.W., Welch, W.R., Scully, R.E. and Wojciechowski, C.A. Ovarian cancer and talc: a case-control study. Cancer. 50(2):372-76, 1982; Booth, M., Beral, V. and Smith, P. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 60(4):592-98, 1989; Chang, S. and Risch, H.A. Perineal talc exposure and risk of ovarian carcinoma. Cancer. 79(12):2396-401, 1997; Wong, C., Hempling, R.E., Piver, M.S., Natarajan, N. and Mettlin, C.J. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol. 93(3):372-76, 1999; Tzonou, A., Polychronopoulou, A., Hsieh, C.C., *et al.* Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer. 55(3):408-10, 1993; Harlow, B.L. and Weiss, N.S. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am J Epidemiol. 130(2):390-94, 1989; Harlow, B.L., Cramer, D.W., Bell, D.A. and Welch, W.R. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol. 80(1):19-26, 1992; Ness, R.B., Grisso, J.A., Cottreau, C., *et al.* Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology. 11(2):111-17, 2000; Godard, B., Foulkes, W.D., Provencher, D., *et al.* Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. Am J Obstet Gynecol. 179(2):403-10, 1998; Cook, L.S., Kamb, M.L. and Weiss, N.S. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol. 145(5):459-65, 1997; Purdie, D., Green, A., Bain, C., *et al.* Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int J Cancer. 62(6):678-84, 1995; Cramer, D.W., Liberman, R.F., Titus-Ernstoff, L., *et al.* Genital talc exposure and risk of ovarian cancer. Int J Cancer. 81(3):351-6, 1999; Cramer, D.W., Titus-Ernstoff, L., McKolanis, J.R., *et al.* Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-31, 2005; Wu, A.H., Pearce, C.L., Tseng, C.C., Templeman, C. and Pike, M.C. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer. 124(6):1409-15, 2009; Moorman, P.G., Palmieri, R.T., Akushevich, L., Berchuck, A. and Schildkraut, J.M. Ovarian cancer risk factors in African-American and white women. Am J Epidemiol. 170(5):598-606, 2009; Mills, P.K., Riordan, D.G., Cress, R.D. and Young, H.A. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int J Cancer. 112(3):458-64, 2004; Merritt, M.A., Green, A.C., Nagle, C.M. and Webb, P.M. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int J Cancer. 122(1):170-76, 2008; Jordan, S.J., Green, A.C., Whiteman, D.C. and Webb, P.M. Risk factors for benign serous and mucinous epithelial ovarian tumors. Obstet Gynecol. 109(3):647-54, 2007; Kurta, M.L., Moysich, K.B., Weissfeld, J.L., *et al.* Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. Cancer Epidemiol Biomarkers Prev. 21(8):1282-92, 2012; Cramer, D.W. and Xu, H. Epidemiologic evidence for uterine growth factors in the

pathogenesis of ovarian cancer. Ann Epidemiol. 5(4):310-14, 1995; Cramer, D.W., Vitonis, A.F., Terry, K.L., Welch, W.R. and Titus, L.J. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. Epidemiology. 27(3):334-46, 2016; Gates, M.A., Tworoger, S.S., Terry, K.L., *et al.* Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 17(9):2436-44, 2008; Schildkraut, J.M., Abbott, S.E., Alberg, A.J., *et al.* Association between Body Powder Use and Ovarian Cancer: the African American Cancer Epidemiology Study (AACES). Cancer Epidemiol Biomarkers Prev. 25(10):1411-17, 2016; Whittemore, A.S., Wu, M.L., Paffenbarger, R.S., Jr., *et al.* Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol. 128(6):1228-40, 1988; Wu, A.H., Pearce, C.L., Tseng, C.C. and Pike, M.C. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 24(7):1094-100, 2015.

[b] Denotes case selection was hospital (H)- or population (P)-based.

[c] Refers to perineal / genital talc application (when evaluated) or other as specified and corresponds to the exposure category for which the OR was derived; default was never/ever for consistent OR comparisons; not intended to characterize whether any metric of dose-response was evaluated.

[d] -Dose-response catergorization captures whether any metric of dose-response was evaluated. - Indicates reference did not evaluate dose response; if dose-response was evaluated, no, yes, and borderline reflect observed relationship, with borderline indicating response was only observed at the highest metric of exposure.

[e] Reported estimate is after adjustment for known confounding variables.

5. Animal carcinogenicity studies of talc

No animal study has ever associated talc exposure with ovarian cancer even though talc has been tested in a wide variety of animal studies.

Most animal studies observed no relationship between talc exposure and cancer (of any kind). Importantly to the current subject matter, the carcinogenicity of talc has been tested by administering it through many different routes and different species without any association with ovarian cancer. For example:

- No ovarian tumors were seen when talc was directly implanted on ovaries (10 mg/ovary) in rats studied for 18 months[63] (a similar study observed ovarian tumors within 6 months of implantation of the known carcinogen dimethylbenz[a]anthracene).[64]
- No ovarian cancer (or any other type of cancer) was observed following an inhalation study of Johnson's Baby Powder in hamsters. In addition, the study design included specific histopathological analysis of the ovary from all animals – with no changes of the ovary observed. Hamsters were exposed to 8.1 mg/m^3, 30 or 150 min/day, 5 days/week, for 300 days in whole-body chambers, and maintained for observation for the remainder of their natural lifespan, with survivors in all groups sacrificed when the number of deaths exceeded 90% in any group.[65] These animals were exposed in whole-body chambers, designed to generate the same exposure concentration throughout the chamber (i.e., not just in the breathing zone of the animal). The rationale for a uniform exposure concentration throughout the whole-body chamber is that the animal will inhale the same dose regardless of where it is positioned and is free to move around anywhere in the cage during exposure. The implication of uniform exposure atmospheres for particulates is that an airborne concentration of test material (in this case talc baby powder) is maintained for the duration of exposure, which results in some particles settling and coating (dusting) all surfaces within the chamber – including the surface of the animal (and the perineum).
- No ovarian cancer was associated with two-year (lifetime) exposures in rats and mice exposed in the NTP inhalation studies, whose study design resulted in both inhalation and body dusting exposures. Specifically, the animals were exposed to talc atmospheres of up to 18 mg/m^3, 6 hr/day, 5 days/week in whole-body exposure chambers.[66] These exposures occurred in whole-body chambers, immersing the animals in the talc exposure atmosphere for 6 hr/day, which would have dusted the entire animal (including the

[63] Hamilton, T.C., Fox, H., Buckley, C.H., Henderson, W.J. and Griffiths, K. Effects of talc on the rat ovary. Br J Exp Pathol. 65(1):101-06, 1984.
[64] Chuffa, L.G.A., Fioruci-Fontanelli, B.A., Mendes, L.O., *et al.* Characterization of Chemically Induced Ovarian Carcinomas in an Ethanol-Preferring Rat Model: Influence of Long-Term Melatonin Treatment. PLOS ONE. 8(12):e81676, 2013.
[65] Wehner, A.P., Zwicker, G.M., Cannon, W.C., Watson, C.R. and Carlton, W.W. Inhalation of talc baby powder by hamsters. Food Cosmet Toxicol. 15(2):121-9, 1977.
[66] NTP. Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N Rats and B6C3f$_1$ Mice (Inhalation Studies). Report No.: NTP TR 421. September, 1993.

perineum, as discussed above). Examination of lung and ovarian tissues from rats and mice from these studies observed talc particles in the lung, but not ovarian, tissues.[67]

- No neoplastic changes were observed in a "preliminary" rat study following intravaginal instillation of talc (100 mg in 0.5 mL, applied daily for three months) or perineal application of a suspension of talc (100 mg in 0.5 mL, applied as an aerosol daily for three months).[68]

IARC's evaluation of talc reviewed carcinogenicity studies in mice (exposed via inhalation exposure, intrathoracic, intraperitoneal and subcutaneous injection); rats (exposed via inhalation exposure, intrathoracic injection, intraperitoneal injection, oral administration and intrapleural and ovarian implantation); and hamsters (exposed via inhalation exposure and intratracheal injection). Of all these studies, only one (a rat 2-yr inhalation study; National Toxicology Program, 1993; the same study discussed above that did not observe ovarian cancer) observed an increased tumor incidence (malignant lung tumors in females) initially attributed to talc exposure.[69] The IARC Working Group assigned *limited* evidence of animal carcinogenicity based on the results of this single study.[70]

Interpretation of the NTP study of talcum powder toward potential human disease is not consistent with mechanisms widely recognized by inhalation toxicologists. While it is true that the study observed lung tumors in female rats, this response cannot be attributed to talcum powder because most dusts, even the most innocuous, when presented in excessive amounts, produce a spectrum of pulmonary responses from the mechanical effect of particles that cannot be distinguished from the inherent toxicity of the particle. Subsequent to the release of the original NTP report, inhalation toxicologists concluded that lung tumors observed in the rats resulted from a phenomenon called lung overload,[71] which is "*a condition of impaired macrophage mediated clearance of particles in the lung following prolonged high-dose exposures to poorly soluble particles (PSP) of low inherent toxicity*."[72]

Lung overload occurs in rats upon excessive particle load (of any kind, including innocuous particles), such that it significantly impedes macrophage-mediated clearance of

[67] Boorman, G.A. and Seely, J.C. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. Regul Toxicol Pharmacol. 21(2):242-3, 1995.
[68] Keskin, N., Teksen, Y.A., Ongun, E.G., Ozay, Y. and Saygili, H. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Archives of gynecology and obstetrics. 280(6):925-31, 2009.
[69] NTP. Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N Rats and B6C3f$_1$ Mice (Inhalation Studies). Report No.: NTP TR 421. September, 1993.
[70] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.
[71] Carr, C.J. Talc: Consumer Uses and Health Perspectives. Proceedings of a workshop. Bethesda, Maryland, January 31-February 1, 1994. Regul Toxicol Pharmacol. 21(2):211-60, 1995.
[72] Warheit, D.B., Kreiling, R. and Levy, L.S. Relevance of the rat lung tumor response to particle overload for human risk assessment—Update and interpretation of new data since ILSI 2000. Toxicology. 374:42-59, 2016; ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals. Poorly Soluble Particles/Lung Overload. 2013. Technical Report No., 122.

particles.[73] Impaired clearance leads to a number of effects that characterize overload; these include an increased transfer of particles to lymph nodes, accumulation of particles in the lung, increases in lung weight, pulmonary inflammation, epithelial hyperplasia (proliferation), fibrosis and eventually cancer (in the rat).[74] A panel of experts at the 1994 International Society of Regulatory Toxicology & Pharmacology and the FDA issued a statement that "*Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans, and the possible conditions of customary human exposures, the NTP Bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk.*[75] The FDA subsequently noted this position in a 2014 correspondence, writing that "*the 1993 NTP study has no relevance to human risk*."[76] Therefore, it is unknown whether the increased lung tumor incidences have any relationship to potential human disease. IARC acknowledged this as well: "*it is not known to what extent humans are susceptible to particle-induced lung cancers associated with titanium dioxide, carbon black, or talc*."[77]

i) Drs. Plunkett and Zelikoff fail to acknowledge talc tumors observed in female rats were attributed to the amount of particles in the lung rather than any inherent hazard of the talc; extrapolation of tumors initiated by lung overload to a general property of smaller doses of the material is scientifically invalid

Scientific literature regarding difficulties interpreting particle-induced lung cancers associated with lung overload conditions in rodents was absent from plaintiffs' experts' opinions. For example, Dr. Plunkett stated that "*the [NTP] study provides important information on talc toxicity that is relevant to assessing the risks of cancer in humans,*"[78] without acknowledging the scientific body of evidence regarding lung overload conditions that existed during the study and how lung overload conditions complicate extrapolation of effects to humans. Similarly, Dr. Zelikoff did not mention how lung overload may have affected the study outcome when she stated, "*Authors of that study speculated these effects could be due to cytokines released from macrophages or a nonspecific effect of the stress of inflammation*."[79] Drs. Plunkett and Zelikoff failed to acknowledge the known difficulties of extrapolating animal results to humans,

[73] Warheit, D.B., Kreiling, R. and Levy, L.S. Relevance of the rat lung tumor response to particle overload for human risk assessment—Update and interpretation of new data since ILSI 2000. Toxicology. 374:42-59, 2016.
[74] Bevan, R.J., Kreiling, R., Levy, L.S. and Warheit, D.B. Toxicity testing of poorly soluble particles, lung overload and lung cancer. Regulatory Toxicology and Pharmacology. 100:80-91, 2018; Warheit, D.B., Kreiling, R. and Levy, L.S. Relevance of the rat lung tumor response to particle overload for human risk assessment—Update and interpretation of new data since ILSI 2000. Toxicology. 374:42-59, 2016.
[75] Carr, C.J. Talc: Consumer Uses and Health Perspectives. Proceedings of a workshop. Bethesda, Maryland, January 31-February 1, 1994. Regul Toxicol Pharmacol. 21(2):211-60, 1995.
[76] Food and Drug Administration. Response from the FDA to Dr. Epstein regarding Citizen Petitions requesting cosmetic talc products be labeled with a cancer warning. Re Docket No. 94P-0420 and FDA-2008-P-0309-0001/CP; 2014.
[77] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010., p. 171.
[78] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 41, Appendix C (ILSI, 2000; Warheit, 2016)
[79] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 16.

particularly given the lung overload conditions observed in the NTP study. Their lack of critical analysis of this complicated issue renders their analyses and their conclusions about potential effects of lesser doses of talc for humans methodologically and critically flawed.

In addition, Dr. Plunkett is incorrect when she states that rats and mice exposed in the NTP studies were exposed in such a way that "*would severely limit any perineal exposure to talc*."[80] As described above, studies were conducted in whole-body inhalation units, which results in the test material (talc baby powder) dusting the entire animal (including the perineum). Although the perineal exposures are unknown, some dusting and perineal transfer would be expected with the animal's persistence in the airborne environment, from the animal rubbing on dusted cage surfaces and from the animal's grooming activities, both during and after daily exposures. Boorman and Seely (1995) noted that "*since animals were exposed for 6 hours per day with talc covering the fur and cage bars, there was ample opportunity for perineal as well as oral and respiratory exposure.*" [81]

ii) Dr. Crowley was scientifically incorrect when he stated there was no animal model for ovarian cancer

Dr. Crowley was scientifically incorrect when he stated there was no animal model for ovarian cancer.[82] He acknowledged that "*NTP is extraordinarily thorough,*"[83] but failed to recognize NTP carcinogenicity studies have identified several agents exhibiting positive or clear evidence of carcinogenicity in the ovaries of rodent models.[84] These chemicals include 5-nitroacenaphthene,[85] 1,3-butadiene,[86] benzene,[87] 4-vinylcyclohexene,[88] nitrofurazone,[89]

[80] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 41.
[81] Boorman, G.A. and Seely, J.C. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. Regul Toxicol Pharmacol. 21(2):242-3, 1995.
[82] Deposition of Michael Crowley, PhD, 1/4/19, 279:7-8.
[83] Deposition of Michael Crowley, PhD, 1/4/19, 277:23-24.
[84] NTP. Organ Sites with Neoplasia. https://manticore.niehs.nih.gov/organsites/. Accessed: 2/1/2019.
[85] NCI. Bioassay of 5-nitroacenaphthene for possible carcinogenicity (CAS No. 602-87-9). Bethesda, MD. National Institutes of Medicine, Report No.: NCI-CG-TR-118. 1978.
[86] National Toxicology Program and National Institutes of Health. NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). Research Triangle Park, NC. NTP 83-071, NIH Publ No 84-2544. Report No.: 288. August, 1984; NTP. Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 434. May, 1993.
[87] NTP. Toxicology and carcinogenesis studies of benzene (CAS No. 71-43-2) in F344/N rats and B6C3F1 mice (gavage studies). Technical report series no. 289. Research Triangle Park, NC. NIH, National Toxicology Program technical report series. April, 1986.
[88] NTP. Toxicology and carcinogenesis studies of 4-vinylcyclohexene (CAS No. 100-40-3) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle, NC. National Institutes of Health, Report No.: NTP TR 303. August, 1986.
[89] NTP. Toxicology and carcinogenesis studies of nitrofurazone (CAS 59-87-0) in male F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 337. June, 1988.

nitrofurantoin,[90] n-methylolacrylamide,[91] 4-vinyl-1-cyclohexene diepoxide,[92] urethane,[93] and acrylamide.[94]

6. Assessment of Bradford Hill criteria for potential talc causation of ovarian cancer

The purpose of a Bradford Hill review is to evaluate a potential association as a means of assessing whether a causal relationship may exist. As described earlier, human epidemiology data can establish whether an association may exist between an exposure and disease but an association is not sufficient to establish causation. An overall conclusion regarding causation is made only after the current generally accepted scientific knowledge is evaluated for each of the Bradford Hill criteria.

a. Strength of association

The scientific dataset supports at most a weak conclusion regarding the strength of association between perineal talc use and ovarian cancer. This is based on the following:

- Observation of a statistically significant association between perineal talc use and ovarian cancer occurred in only about half of the case-control studies and the majority of those had used population-based case selection methodology. Only two of the nine[95] unique hospital-based case populations (or 22%) observed statistically significant associations compared to observation of statistically significant associations in ten of the 19[96] unique population-based case populations (53%). Investigators have hypothesized that the tendency for positive associations to occur in population-based case selection studies may be due to (1) recall bias, with population-based patients having time (post-discharge and before interview) to review literature about suspected causes of ovarian cancer that hospital based-cases may not have; or (2) a treatment effect, which is essentially that population-based cases may not adequately differentiate when talc use began (i.e., before or after therapeutic interventions).[97] A statistically significant association was observed

[90] NTP. Toxicology and carcinogenesis studies of nitrofurantoin (CAS No. 67-20-9) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 341. September, 1989.
[91] NTP. Toxicology and carcinogenesis studies of n-methylolacrylamide (CAS No. 924-42-5) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 352. September, 1989.
[92] NTP. Toxicology and carcinogenesis studies of 4-vinyl-l-cyclohexene diepoxide (CAS No. 106-87-6) in F344/N rats and B6C3F1 mice (dermal studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 362. November, 1989.
[93] NTP. Toxicology and carcinogenesis studies of urethane, ethanol, and urethane/ethanol (urethane, CAS No. 51-79-6; ethanol, CAS No. 64-17-5) in B6C3F1 mice (drinking water studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 510. August, 2004.
[94] NTP. Toxicology and carcinogenesis studies of acrylamide (CAS No. 79-06-1) in F344/N rats and B6C3F1 mice (feed and drinking water studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 575. July, 2012.
[95] The case-control populations reported in Cramer et al., 1982 and Harlow et al., 1992 were combined in the analysis presented by Cramer et al., 1995.
[96] The case-control population reported in Wu et al., 2015 also included the population previously reported in Wu et al., 2009.
[97] Muscat, J.E. and Huncharek, M.S. Perineal talc use and ovarian cancer: a critical review. Eur J Cancer Prev. 17(2):139-46, 2008.

when studies were combined in a meta-analysis, but as discussed above, the result is of unknown accuracy given that the methods used to select studies for inclusion were flawed, as they included duplicate datasets. None of the cohort studies, regarded as the scientifically stronger study design, replicated the association.

- When observed, increased risk levels were relatively weak (below levels associated with doubling of the risk, and much less than the level of 10 suggested by Hill for strong evidence).

- When observed, increased risk levels were present only in case-control studies, which are more susceptible to bias. Statistically significant increased risks were observed more often in population-based case studies, which are more susceptible to recall bias than hospital-based case studies. Cohort studies, which are inherently less susceptible to bias, did not observe the association. The potential for bias cannot be ruled out as being responsible for associations observed in case-control studies.

b. Consistency of findings

The scientific dataset does not reflect a consistency of findings between perineal talc use and ovarian cancer. This is so because:

- Ovarian cancer has not been observed in animal carcinogenicity studies.

- No statistically significant association was observed in any of the cohort studies.

- Case-control studies only observed a statistically significant association in about half of the studies. The tendency for observation of a statistically significant association in case-control studies differs between hospital- and population-based studies. Although a statistically significant association was observed when studies were combined in a meta-analysis, failure of the cohort studies to replicate the association made these results uncertain.

c. Specificity of association

The scientific dataset lacks specificity of the association between perineal talc use and ovarian cancer. To the contrary, relatively low ORs indicate that: (1) many women who had ovarian cancer never used talc; and (2) many women who used talc did not have ovarian cancer.

d. Temporal sequence

The temporal sequence between perineal talc use and ovarian cancer is unknown. More than 60% of patients have advanced disease at the time they are diagnosed, and ovarian cancer latency (or how long it takes to develop) is unknown.[98] Thus, it is impossible to ascertain the relevant exposure period for any potential causative agent once disease status has been diagnosed. Cohort studies, where both exposure and null disease status are known for women who are then followed over time, have failed to find a statistically significant association.

[98] Bhoola, S. and Hoskins, W.J. Diagnosis and management of epithelial ovarian cancer. Obstet Gynecol. 107(6):1399-410, 2006.

e. Biological gradient

Biological gradients are typically established through demonstration of a dose-response relationship. No biological gradient has been scientifically established for talc. Specifically, of the 15 studies that observed a statistically significantly increased risk (see Table 5), a third of the studies reviewed (4/15 or 27%) did not observe any effect with dose and 4/15 (27%) only evaluated use as ever vs never, which provides no information for dose-response assessment. Of the studies that evaluated dose-response, three observed a borderline dose-response relationship and three observed a dose-response relationship (Cramer et al., 2016,[99] Wu et al., 2009,[100] Wu et al., 2015,[101] and Schildkraut et al., 2016).[102] Note only three studies were counted of the four publications because Wu et al. (2009 and 2015) reported overlapped datasets and only one (Wu et al., 2009) included information regarding frequency and duration of use.[103] Overall, for the studies that observed a positive association between perineal talc use and ovarian cancer risk, only 6/15 (40%) exhibited results consistent with a biological gradient of effect. Recent results of a meta-analysis of 24 case-control studies do not clarify the issue. The review identified 5/24 studies where dose could be defined as the approximate total number of applications, with 3,600 selected as a cut-point to separate groups that had used talcum powder approximately one time daily for less than or more than 10 years. Resulting ORs were similar (and statistically not different),[104] which does not support the existence of a biological gradient of response for perineal talc application and ovarian cancer.

f. Biological or theoretical plausibility

In assessing the factor of biological plausibility, two main issues regarding biological plausibility must come into play: (1) does scientific data show talc can traverse from the external perineal region to the ovaries; and (2) if talc reaches the ovaries by any route, is it an ovarian carcinogen?

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[99] Cramer, D.W., Vitonis, A.F., Terry, K.L., Welch, W.R. and Titus, L.J. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. Epidemiology. 27(3):334-46, 2016.
[100] Wu, A.H., Pearce, C.L., Tseng, C.C., Templeman, C. and Pike, M.C. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer. 124(6):1409-15, 2009.
[101] Wu, A.H., Pearce, C.L., Tseng, C.C. and Pike, M.C. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 24(7):1094-100, 2015.
[102] Schildkraut, J.M., Abbott, S.E., Alberg, A.J., *et al.* Association between Body Powder Use and Ovarian Cancer: the African American Cancer Epidemiology Study (AACES). Cancer Epidemiol Biomarkers Prev. 25(10):1411-17, 2016.
[103] Wu, A.H., Pearce, C.L., Tseng, C.C., Templeman, C. and Pike, M.C. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer. 124(6):1409-15, 2009; Wu, A.H., Pearce, C.L., Tseng, C.C. and Pike, M.C. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 24(7):1094-100, 2015; Penninkilampi, R. and Eslick, G.D. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. Epidemiology Epidemiology. 29(1):41-49, 2018.
[104] Penninkilampi, R. and Eslick, G.D. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. Epidemiology Epidemiology. 29(1):41-49, 2018.

i) Scientific dataset for perineal talc to travel to ovarian tissue

None of the animal studies evaluate whether transport of talc can occur following powder applications to the perineum, although as described below, one "preliminary" study evaluated transport following an aerosol perineal application of an aqueous suspension of talc.[105] The perineum is the exterior surface area between the thighs extending from the coccyx [tailbone] to the pubis that includes the anus and external genitalia.[106] In order for talc to transverse from the external application at the perineal region, it must physically travel into/through vagina, cervix, uterus, fallopian tube, exit the fimbriae and then deposit on the ovary (see anatomical cross section in Figure 1). Studies evaluating installations directly into the vagina or the uterus fail to capture whether talc can travel from the perineal region to that site of application (i.e., vagina or uterus).

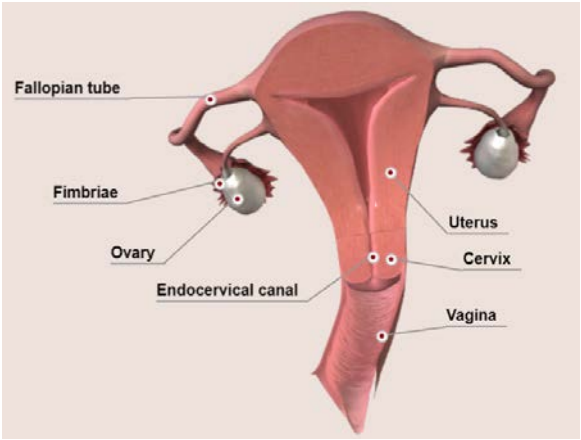

Figure 1. Human Female Reproductive Tract

Regardless of this deficiency, studies have investigated the potential for talc to traverse to the ovary once manually inserted into the reproductive canal. Some studies have reported migration up the reproductive canal and others have not, including:

- In a study of rats by Henderson et al. (1986), rats received intrauterine instillations of 25 mg (0.25 mL) once (and sacrificed after five days) or multiple times (up to four additional treatments with sacrifices occurring up to Day 49). Investigators reported talc was observed in ashed (i.e., incinerated) ovarian tissue in all groups of rats following intrauterine instillations, but no quantitation was provided.[107]
- The same study (Henderson et al., 1986) also instilled 25 mg (0.25 mL) of talc into the vagina of rats, which were sacrificed after up to four days following treatment. No talc was detected in ashed (i.e., incinerated) ovarian tissue in rats following intravaginal instillations.[108]

[105] Keskin, N., Teksen, Y.A., Ongun, E.G., Ozay, Y. and Saygili, H. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Archives of gynecology and obstetrics. 280(6):925-31, 2009.
[106] Perineum. In: Farlex Partner Medical Dictionary. https://medical-dictionary.thefreedictionary.com/perineum. Accessed: January 12, 2019.
[107] Henderson, W.J., Hamilton, T.C., Baylis, M.S., Pierrepoint, C.G. and Griffiths, K. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ Res. 40(2):247-50, 1986.
[108] Henderson, W.J., Hamilton, T.C., Baylis, M.S., Pierrepoint, C.G. and Griffiths, K. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ Res. 40(2):247-50, 1986.

- No radiolabeled talc was detected in rabbit ovaries three days following six daily doses of radiolabeled talc applied to the vagina (0.5 mL; talc dose unclear), but small levels were detected in the uterus and fallopian tubes.[109]
- No radiolabeled talc was detected in monkey ovaries following direct application of 125 mg (0.3 mL) radiolabeled talc to the vagina (30 applications in 45 days). A control group was utilized. Radiolabeled talc was detected only in the vagina and cervix of dosed monkeys.[110]
- A "preliminary" study evaluated rats following intravaginal instillation (100 mg in 0.5 mL, applied daily for three months) or perineal application of a suspension (100 mg in 0.5 mL, applied as an aerosol daily for three months to rats weighing 200-250 g [equivalent to 400 mg/kg or 24 g daily to the perineal region for a 60 kg or 132 lb woman], no details given regarding force of the aerosol, application rate or area). The authors concluded that talc was associated with foreign body reaction and infection. However, infection (vaginitis) was observed in both control and exposed groups when the study began, which indicates infection may be attributable to animal housing conditions rather than any study exposures. In addition, no details were given regarding "foreign body reaction," the severity of the reaction, or whether it was present or absent in controls.[111]

Animal studies do not provide any scientific evidence that talc can translocate to the ovary when applied externally at the perineum. Animal studies have sometimes observed retrograde transport of particles through the reproductive canal and suggested that if talc particles are injected directly into the vagina or uterus, there may be a mechanism for translocation to the ovaries.

A few studies have detected talc particles in ovarian tumors and tissue of humans, but the source of the detected talc particles is unclear. Specifically, the first study that reported the presence of talc within human ovarian tumor tissue[112] was criticized for the possibility that surgeons' use of talc-dusted gloves had contaminated samples.[113] The same group published a follow-up letter that indicated similar talc burden in all types of ovarian tissue analyzed (normal, cystic and adenocarcinomas).[114] Importantly, tissues had not been analyzed directly; they had

[109] Phillips, J.C., Young, P.J., Hardy, K. and Gangolli, S.D. Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. Food and Cosmetics Toxicology. 16(2):161-63, 1978.
[110] Wehner, A.P., Weller, R.E. and Lepel, E.A. On talc translocation from the vagina to the oviducts and beyond. Food Chem Toxicol. 24(4):329-38, 1986.
[111] Keskin, N., Teksen, Y.A., Ongun, E.G., Ozay, Y. and Saygili, H. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Archives of gynecology and obstetrics. 280(6):925-31, 2009.
[112] Henderson, W.J., Joslin, C.A., Turnbull, A.C. and Griffiths, K. Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol Br Commonw. 78(3):266-72, 1971.
[113] Henderson, W.J., Hamilton, T.C. and Griffiths, K. Talc in normal and malignant ovarian tissue. Lancet. 1(8114):499, 1979.
[114] Henderson, W.J., Hamilton, T.C. and Griffiths, K. Talc in normal and malignant ovarian tissue. Lancet. 1(8114):499, 1979.

first been prepared in paraffin (wax) blocks. Tissue blocks were rehydrated prior to talc visualization. Potential for contamination could not be assessed from the data presented.

A subsequent study published nearly two decades later analyzed ovarian tissue from women for whom their talc history (in terms of numbers of lifetime perineal applications) was known. The authors indicated some controls were incorporated into the study design. They observed talc particles in ovaries from both groups of women: (1) those with histories of perineal application and (2) those with no history of perineal application. Particle counts "*were completely unrelated to reported levels of perineal talc exposure*."[115]

Although talc has been found in ovarian tissue (as described above), it is unclear if studies had eliminated sources of talc contamination. In addition, its presence, if accurate, was not related to perineal application, making any support for a potential causal relationship between perineal application and ovarian cancer implausible.

The inconsistent results of talc transport studies are consistent with a weak rating for biological or theoretical plausibility. IARC agrees with this assessment, as following its review, the Working Group concluded that evidence for retrograde transport of talc to the ovaries in normal women was weak and that studies in animals (including rodents and non-human primates) showed no evidence of retrograde transport of talc to the ovaries.[116]

ii) Scientific dataset for talc as an ovarian carcinogen

The issue of the carcinogenicity for talc was addressed above. Talc has not been shown to be an ovarian carcinogen (or to cause a specific, talc-related tumorigenic response in animal studies). Animal studies do not support the theory that ovarian cancer can be caused by talc, given that no animal studies have observed an ovarian cancer hazard for talc exposure, most carcinogenicity studies fail to observe any cancer response, and the probability that lung tumors were observed in the NTP study simply due to particle overload rather than any intrinsic property of talc.

Plaintiffs' experts, Drs. Carson,[117] Crowley,[118] Plunkett[119] and Zelikoff[120] all hypothesize that inflammation, purportedly induced by talc particles, extends biological plausibility to ovarian carcinogenesis. However, although inflammation and associated oxidative stress can be related to carcinogenesis, sites for which inflammatory mechanisms have been implicated in tumorigenesis and progression do not include ovarian cancer. Sites known to be susceptible for inflammatory-mediated cancer development are currently limited to stomach, colon, skin, liver,

[115] Heller, D.S., Westhoff, C., Gordon, R.E. and Katz, N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol. 174(5):1507-10, 1996.
[116] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.
[117] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 4, 5, 10.
[118] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 15.
[119] Expert Report of Laura M. Plunkett, PhD, DABT, 11/16/18, p. 19-20, 45-47.
[120] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 19-26.

breast, lung and head/neck cancers.[121] Inflammation remains a hypothesized mechanism for ovarian cancer, as conditions associated with increased inflammation (recurrent ovulation, pelvic inflammatory disease, obesity) have observed inconsistent associations and inflammation, as a mechanism for ovarian cancer, warrants further investigation.[122] A recent publication by Dr. Saed indicated that while "*oxidative stress may play a role in maintaining the oncogenic phenotype of ovarian cancer cells*," the "*exact origin(s) and pathogenesis of ovarian cancer still remains under debate*."[123] Chronic use of anti-inflammatory drugs (aspirin or non-aspirin non-steroidal anti-inflammatory drugs [NSAIDs]) has not been demonstrated to reduce the risk of ovarian cancer.[124] Because scientific research regarding the role of inflammation and ovarian cancer causation remains a hypothesis under investigation, a compound's propensity (when given at a high enough dose) to induce inflammation is of unknown relevance to the biological plausibility of talc to cause ovarian cancer. This is also important because, as discussed below, the inflammatory response induced by talc pleurodesis in the lung has not been associated with cancer.

Talc pleurodesis is a medical procedure in which cosmetic or pharmaceutical-grade talc is introduced directly into the pleural space, where it induces an acute inflammatory response to stimulate scarring and subsequently to eliminate the pleural space. Pleurodesis has been used as a medical treatment for pneumothorax (air in the pleural space) or pleural effusion (fluid in the pleural space). No mesotheliomas have been reported in follow-up of these patients for up to 40 years after treatment.[125] Plaintiffs' expert Dr. Plunkett asserts that the known inflammatory responses observed in the "*pleurodesis literature provide further support for inflammation as a known tissue response to talc, even though the type of inflammatory response produced in the pleurodesis procedures is acute, not a chronic response as is characteristic of carcinogenesis*."[126] However, talc particles remain in the pleural space of the lungs of patients, where they provide a chronic exposure to cells therein (without a carcinogenic response). The absence of malignancy in talc pleurodesis patients undermines the suggestion that a chronic inflammatory response induced by talc particles can cause cancer.[127]

Dr. Zelikoff's allegation that talc increases ovarian cancer risk through reducing immunity to MUC1 is not a generally accepted mechanism associated with the development of

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[121] Munn, L.L. Cancer and inflammation. Wiley interdisciplinary reviews Systems biology and medicine. 9(2), 2017.
[122] Webb, P.M. and Jordan, S.J. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 41:3-14, 2017.
[123] Saed, G.M., Diamond, M.P. and Fletcher, N.M. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. Gynecol Oncol. 145(3):595-602, 2017.
[124] Trabert, B., Poole, E.M., White, E., *et al.* Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium. J Natl Cancer Inst. 111(2):137-45, 2019.
[125] Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit. A survey of the long-term effects of talc and kaolin pleurodesis. Br J Dis Chest. 73(3):285-88, 1979; Viskum, K., Lange, P. and Mortensen, J. Long term sequelae after talc pleurodesis for spontaneous pneumothorax. Pneumologie. 43(2):105-06, 1989.
[126] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 48.
[127] Finley, B.L., Benson, S.M. and Marsh, G.M. Cosmetic talc as a risk factor for pleural mesothelioma: a weight of evidence evaluation of the epidemiology. Inhal Toxicol. Mar, 29(4):179-85, 2017.

ovarian cancer.[128] MUC1 is a membrane-bound glycoprotein present on most epithelial cells. Its overexpression is a "*prominent characteristic of various types of cancers and inflammatory diseases*," including ovarian cancer.[129] In cancer patients, higher levels of anti-MUC1 antibodies correlate with better prognosis, suggesting that anti-MUC1 antibody levels may be associated with increased immunity against tumors expressing MUC1. Information cited by Zelikoff (Karageorgi et al., 2010) is an investigation of endometrial cancer risk that cites back to the original publication that investigated the hypothesis that anti-MUC1 antibodies may be related to various risk factors (e.g., race, religion, marital status, pregnancy, smoking, etc.).[130] That study (Cramer et al., 2005) assessed circulating levels of anti-MUC1 antibodies in 705 women without ovarian cancer. They observed a slight statistical association between "*nonuse of talc in genital hygiene*" and increased circulating levels of anti-MUC1 antibodies.[131] However, any potential association between circulating anti-MUC1 antibodies and subsequently developing ovarian cancer is unknown, making the association of unknown relevance to ovarian cancer development and risk. Reliance on this study to draw an opinion on ovarian cancer risk is scientifically flawed and methodologically invalid.

g. Coherence with established knowledge

Support for the remaining criteria – coherence with established knowledge and the ability to draw analogies between related chemicals – is hindered by the lack of agents causally related to ovarian cancer to which comparisons can be made. Effects of a potential intervention (eliminating perineal talc use) are likewise unknown.

The overall assessment for talc against the Bradford Hill criteria is provided in Table 6. Current scientific knowledge provides only weak support for several and strong support for none of the criteria, which does not provide the basis to support an overall conclusion of a causal relationship between perineal talc use and ovarian cancer.

[128] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 19.
[129] Bafna, S., Kaur, S. and Batra, S.K. Membrane-bound mucins: the mechanistic basis for alterations in the growth and survival of cancer cells. Oncogene. 29(20):2893-904, 2010; Deng, J., Wang, L., Chen, H., *et al.* The role of tumour-associated MUC1 in epithelial ovarian cancer metastasis and progression. Cancer metastasis reviews. 32(3-4):535-51, 2013; Karageorgi, S., Gates, M.A., Hankinson, S.E. and De Vivo, I. Perineal use of talcum powder and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev. 19(5):1269-75, 2010; Cramer, D.W., Titus-Ernstoff, L., McKolanis, J.R., *et al.* Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-31, 2005.
[130] Karageorgi, S., Gates, M.A., Hankinson, S.E. and De Vivo, I. Perineal use of talcum powder and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev. 19(5):1269-75, 2010; Cramer, D.W., Titus-Ernstoff, L., McKolanis, J.R., *et al.* Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-31, 2005.
[131] Cramer, D.W., Titus-Ernstoff, L., McKolanis, J.R., *et al.* Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-31, 2005.

Table 6. Bradford Hill Criteria Assessment for Talc

Criteria	Assessment
1. **Strength of association.** Hill suggested that strong associations support a causal relationship (for example, a 10x increase in death rate could serve as strong evidence in favor of a potential relationship). Hill was careful not to dismiss modest changes.	Weak
2. **Consistency of findings.** Hill recommended results be replicated in different studies, and advocated using different experimental approaches that could reach similar conclusions.	Not established
3. **Specificity of association.** Likelihood of a cause and effect relationship is strengthened by how tightly linked an outcome is to the exposure.	Weak
4. **Temporal sequence.** Cause must occur before the effect.	Unknown
5. **Biological gradient.** Establishment of a clear dose-response relationship, such that greater exposure is linked to a more severe outcome provides further causation support.	Not established
6. **Biological or theoretical plausibility**. The ability to postulate a reasonable mechanism of action can strengthen the likelihood of causation. This does not, however, address the potential that the current state of knowledge is limited.	Weak
7. **Coherence with established knowledge**. The association between the cause and effect should reasonably align with the current understanding of disease pathogenesis.	Unknown disease pathogenesis
Other criteria: 1. Support from a decreased incidence of disease following an intervention to limit exposure. 2. The ability to draw analogies between related chemicals can lessen the depth of experimental validation.	Unknown

G. ASSESSMENT OF ALLEGED CONTAMINANTS IN JOHNSON'S BABY POWDER AND SHOWER TO SHOWER

1. Asbestos

a. Key opinions

- Scientific studies do not support the theory that asbestos, as an alleged contaminant in talc, causes ovarian cancer in women.
- Regulations that ensure asbestos levels will protect people from asbestos-related mesothelioma will also protect people from any asbestos-related ovarian cancer.
- If talcum products contained asbestos fibers at the maximum level alleged by Drs. Longo and Rigler, concentrations would not be significant or meaningful to human health; exposure estimation using conservative assumptions of all other factors (use, frequency,

duration) results in 50-year cumulative airborne asbestos fiber exposures that are three times below those associated with ambient, background exposure; at least 4,000 times below those derived working for 50 years at the OSHA PEL; and at least 29,000 times below tremolite asbestos levels considered protective of mesothelioma.

- This analysis supports the conclusion that scientific studies do not show that asbestos, as an alleged contaminant in talc, causes ovarian cancer in women.

b. Definitions

The term "asbestos" is a generic term that specifically refers to a group of six naturally-occurring, highly fibrous, regulated, and commercialized members of the amphibole and serpentine mineral classes, listed in Table 7.[132] Asbestos refers to the asbestiform variety of each of the six minerals listed in Table 7.

Table 7. Asbestos names

Mineral type	Regulated fiber type	Mineral name	Composition[133]
Serpentine	Chrysotile	Chrysotile	$Mg_3Si_2O_5(OH)_4$
Amphibole	Tremolite asbestos	Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
Amphibole	Actinolite asbestos	Actinolite	$Ca_2(Mg,Fe^{+2})Si_8O_{22}(OH)_2$
Amphibole	Anthophyllite asbestos	Anthophyllite	$Mg_7Si_8O_{22}(OH)_2$
Amphibole	Crocidolite	Riebeckite	$Na_2(Fe^{+2},Mg)_3Fe^{+3}Si_8O_{22}(OH)_2$
Amphibole	Amosite	Cummingtonite-grunerite	$(Fe+2)_2(Fe^{+2},Mg)_5Si_8O_{22}(OH)_2$

Adapted from Wylie, et al. (2015)[134]

Notably, the definition of asbestiform particles denotes both habit (i.e., fibrous growth) and physical properties (bundles whose cleavage results in thinner fibers; flexibility; high length-to-width ratios; etc.).

In this report, the term "asbestos" refers to the regulated fibrous asbestos minerals listed in Table 7 above. Historical exposures to high levels of airborne asbestos demonstrated a clear causal relationship between asbestos and pleural mesothelioma.[135]

[132] OSHA. 29 CFR Parts 1910 and 1926 Occupational Exposure to Asbestos, Tremolite, Anthophyllite and Actinolite – Final Rule. Federal Register. 57(110):24310-31, 1992.
[133] Virta, R.L. Asbestos: Geology, Mineralogy, Mining, and Uses. U.S. Geological Survey, Report No.: 02-149. 2002.
[134] Wylie, A.G. and Candela, P.A. Methodologies for determining the sources, characteristics, distribution, and abundance of asbestiform and nonasbestiform amphibole and serpentine in ambient air and water. J Toxicol Environ Health B Crit Rev. 18(1):1-42, 2015.
[135] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.

c. Human epidemiology

Human epidemiology studies that have evaluated the association between asbestos exposure and ovarian cancer in humans are inconsistent. Dose-response is a key metric for evaluating these results. Some studies showing increased mesothelioma rates in humans occupationally exposed to high levels of asbestos also observed statistically significant (but much lesser) increases in ovarian cancer rates. It follows, then, that if ovarian cancer is associated with asbestos exposure, levels that are not associated with mesothelioma will also not cause ovarian cancer.

Statistically significant associations between asbestos and ovarian cancer have been generally limited to cohorts of women occupationally exposed to historically high levels of asbestos (exposures generally occurred and/or began before the 1960s with cohorts also exhibiting large increases in asbestos-related disease, including mesothelioma). These studies include, but are not limited to:

- London asbestos factory workers;[136]
- Gas mask manufacturers/assemblers who used asbestos in filtration material;[137]
- Employment in an Italian asbestos company manufacturing textiles;[138]
- Asbestos cement workers;[139]
- Yarn and cloth workers (but not for the overall population of asbestos plant manufacturing workers);[140] and
- Chinese textile factory workers (a more recently exposed population) exposed to high levels of asbestos.[141]

Exposure concentrations were seldom included in these publications of studies that reported ovarian cancer. Of those that did:

- Asbestos Cement Workers: The 1971 average concentrations measured in the mixing and production areas of the asbestos cement plant were 303.8 and 13.5 f/cc, respectively;[142] and

[136] Berry, G., Newhouse, M.L. and Wagner, J.C. Mortality from all cancers of asbestos factory workers in east London 1933-80. Occupational and Environmental Medicine. 57(11):782-85, 2000.
[137] Wignall, B.K. and Fox, A.J. Mortality of female gas mask assemblers. Br J Ind Med. 39(1):34-38, 1982.
[138] Pira, E., Romano, C., Violante, F.S., *et al.* Updated mortality study of a cohort of asbestos textile workers. Cancer medicine. 5(9):2623-28, 2016.
[139] Magnani, C., Ferrante, D., Barone-Adesi, F., *et al.* Cancer risk after cessation of asbestos exposure: A cohort study of Italian asbestos cement workers. Occup Environ Med. 65(3):164-70, 2008.
[140] Wilczynska, U., Szymczak, W. and Szeszenia-Dabrowska, N. Mortality from malignant neoplasms among workers of an asbestos processing plant in Poland: Results of prolonged observation. Int J Occup Med Environ Health. 18(4):313-26, 2005.
[141] Wang, X., Lin, S., Yu, I., *et al.* Cause-specific mortality in a Chinese chrysotile textile worker cohort. Cancer Sci. 104(2):245-49, 2013.
[142] Magnani, C., Ferrante, D., Barone-Adesi, F., *et al.* Cancer risk after cessation of asbestos exposure: A cohort study of Italian asbestos cement workers. Occup Environ Med. 65(3):164-70, 2008.

- Chinese Textile Factory Workers: Concentrations in air samples in the raw material and textile sections of the Chinese textile factory were 18 and 6 f/cc (6 and 8 f/cc in personal samples), respectively.[143]

Analyses of human ovarian tissue sometimes report asbestos fibers at detectable levels in surveys of ovarian cancer cases as well as in tissues from women without ovarian cancer.[144] However, detection of fibers in ovaries (of diseased and non-diseased women) provides no information regarding the route, duration, or intensity of exposure; and provides no evidence regarding causation.

Retrospective studies of wives of asbestos cement workers did not observe an increased effect for ovarian cancer associated with their husbands' take-home asbestos exposure, even when the increased effect for pleural malignant mesothelioma death was statistically significantly elevated to 18.0 (95% CI=11.14-27.52) for the wives.[145]

A retrospective cohort that evaluated women with asbestosis (asbestos disease resulting from relatively high exposures) observed a statistically significant association with ovarian cancer mortality for a cohort of Italian women.[146] However, the effect was not observed in Polish women with asbestosis.[147]

Other studies, with presumably lesser exposures, were generally not associated with statistically significantly increased ovarian cancer deaths. It is impossible to ascertain whether the absence of increased ovarian cancer deaths in these studies was because the effect is not causal or if the effect is only associated with excessively high exposure concentrations. For example, these cohorts include a retrospective cohort of all Finnish women occupationally active at the 1970 census (followed through 1995),[148] friction material factory workers,[149] all German workers who had been exposed to asbestos for >3 years before 1977,[150] and workers in Great Britain exposed to asbestos who had worked in factories and workplaces and had been medically examined under the Asbestos Licensing Regulations (1983) or Control of Asbestos at Work

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[143] Wang, X., Lin, S., Yu, I., *et al.* Cause-specific mortality in a Chinese chrysotile textile worker cohort. Cancer Sci. 104(2):245-49, 2013.

[144] Langseth, H., Johansen, B.V., Nesland, J.M. and Kjaerheim, K. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. International Journal of Gynecological Cancer. 17(1):44-49, 2007; Heller, D.S., Gordon, R.E., Westhoff, C. and Gerber, S. Asbestos Exposure and Ovarian Fiber Burden. American Journal of Industrial Medicine. 29(5):435-39, 1996; Heller, D.S., Gordon, R.E. and Katz, N. Correlation of asbestos fiber burdens in fallopian tubes and ovarian tissue. Am J Obstet Gynecol. 181(2):346-7, 1999.

[145] Ferrante, D., Bertolotti, M., Todesco, A., *et al.* Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. Environ Health Perspect. 115(10):1401-05, 2007.

[146] Germani, D., Belli, S., Bruno, C., *et al.* Cohort mortality study of women compensated for asbestosis in Italy. Am J Ind Med. 36(1):129-34, 1999.

[147] Szeszenia-Dabrowska, N., Wilczynska, U., Szymczak, W. and Strzelecka, A. Mortality study of workers compensated for asbestosis in Poland, 1970-1997. Int J Occup Med Environ Health. 15(3):267-78, 2002.

[148] Vasama-Neuvonen, K., Pukkala, E., Paakkulainen, H., *et al.* Ovarian cancer and occupational exposures in Finland. Am J Ind Med. 36(1):83-89, 1999.

[149] Newhouse, M.L. and Sullivan, K.R. A mortality study of workers manufacturing friction materials: 1941 -1986. Br J Ind Med. 46(3):176-79, 1989.

[150] Rösler, J.A., Woitowitz, H.J., Lange, H.J., *et al.* Mortality rates in a female cohort following asbestos exposure in Germany. J Occup Med. 36(8):889-93, 1994.

Regulations (1987).[151] Fiber concentrations, which were seldom assessed in these cohorts, were available in the friction material factory, and ranged from >20 structures/mL (before 1930) to <1 structure/mL (after 1970).[152]

In addition to uncertainties in exposure concentrations, interpretation of epidemiology studies for a possible association between asbestos exposure and ovarian cancer has historically been hindered by the limited numbers of exposed workers (and cases), ascertainment of disease status from cause of death on death certificates, and the potential misdiagnosis of peritoneal mesothelioma cases as ovarian cancer (a limitation that has been reduced following the development of more specific immunohistochemical diagnostic techniques).[153]

Meta-analyses (analyses that combine multiple individual epidemiology studies) have provided inconsistent results for the association between occupational asbestos exposure and ovarian cancer. One analysis attempted to clarify issues regarding disease status/diagnosis through evaluation of all studies published up until 2008 (e.g., 14 cohort and two case-control studies). No statistically significant association for increased ovarian cancer death was observed when the analysis was limited to four studies with confirmed ovarian cancers (1.29, 95% CI=0.97-1.73). A statistically significant effect for increased ovarian cancer death (1.75, 95% CI=1.45-2.10) was only observed when the pool of cases included those with non-confirmed ovarian cancer, suggesting that disease misclassification (e.g., incorrect attribution of ovarian cancer instead of peritoneal mesothelioma) may have biased results, leading investigators to observe an effect when none may be truly present.[154]

Another meta-analysis (evaluating studies published to 2010 that also included some unpublished results) identified 18 cohort studies of women occupationally exposed to asbestos observed a statistically significant increase in ovarian cancer deaths. Pooling the 18 studies resulted in an overall effect for ovarian cancer deaths of 1.77 (95% CI=1.37-2.28). The effect was deemed insensitive of pathologic confirmation, but the authors stated this was of limited significance because pathologic confirmation was available in only two of the 18 studies. In addition, results indicated that effect estimates were strongest among those cohorts most exposed (e.g., those with confirmed asbestosis and for those with lung cancer effect estimates that exceeded 2.0).[155]

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[151] Harding, A.H., Darnton, A., Wegerdt, J. and McElvenny, D. Mortality among British asbestos workers undergoing regular medical examinations (1971-2005). Occup Environ Med. 66:487-95, 2009.
[152] Newhouse, M.L. and Sullivan, K.R. A mortality study of workers manufacturing friction materials: 1941 -1986. Br J Ind Med. 46(3):176-79, 1989.
[153] IARC. Asbestos (chrysotile, amosite, crocidolite, tremolite, actinolite, and anthophyllite). In: Arsenic, Metals, Fibres, and Dusts. IARC Monographs on the Evaluation of the Carcinogenic Risk to Human. Vol 100 part C. Lyon: World Health Organization; 2012. p. 219-310. p. 256; Reid, A., de Klerk, N. and Musk, A.W. Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-Analysis. Cancer Epidemiol Biomarkers Prev. 20(7):1287-95, 2011.
[154] Reid, A., de Klerk, N. and Musk, A.W. Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-Analysis. Cancer Epidemiol Biomarkers Prev. 20(7):1287-95, 2011.
[155] Camargo, M.C., Stayner, L.T., Straif, K., *et al.* Occupational exposure to asbestos and ovarian cancer: a meta-analysis. Environ Health Perspect. 119(9):1211-17, 2011.

In occupational asbestos worker exposure cohorts that showed an increased risk of ovarian cancer mortality, the observed increase in deaths due to mesothelioma was much greater (from 5 to 27 times) than that observed for deaths due to ovarian cancer. For example, the increased (pleural) mesothelioma mortality effect ratios (compared to the general population) for studies that had reported increased ovarian cancer mortalities included cohorts of gas mask manufacturing workers (mesothelioma effect=75, $p<0.01$),[156] Italian asbestos textile workers (pleural mesothelioma effect=60.8, 95% CI=42.6-84.2),[157] asbestos cement workers (pleural malignant neoplasm effect=62.1, 95% CI=44.2-84.9),[158] yarn and cloth asbestos manufacturing workers (pleural mesothelioma effect=22.7, 95% CI=4.7-66)[159] and Chinese textile factory workers (mesothelioma effect=167, 95% CI=29.4-944).[160]

Studies of humans occupationally exposed to high levels of asbestos have, in addition to increased mesothelioma, also occasionally observed statistically significant, but much lesser, effects toward ovarian cancer. It follows, then, that if ovarian cancer is associated with asbestos exposure, levels that are not associated with mesothelioma will not cause ovarian cancer.

d. Alleged levels in Johnson's Baby Powder and Shower to Shower

Even if talcum products contained asbestos fibers and did so at the levels alleged by Drs. Longo and Rigler,[161] such concentrations would not be significant or meaningful compared to allowable workplace exposure levels and the lowest cumulative tremolite asbestos concentration associated with mesothelioma. As detailed later in this section, assuming that the asbestos fibers were present at the maximum concentration alleged by Drs. Longo and Rigler, several comparisons can be made, including:

- The annual average exposure to asbestos fibers from ambient air in the US is more than three times higher than alleged asbestos exposure from talc;
- The OSHA permissible exposure limit (PEL) for asbestos fibers is more than 4,000 times higher than alleged asbestos exposure from talc; and,
- The lowest cumulative tremolite asbestos concentration associated with mesothelioma is more than 29,000 times higher than alleged asbestos exposure from talc.

As shown in Table 9 (see page 49), comparison of the alleged levels to ambient background concentrations, acceptable exposure concentrations, and the lowest cumulative

[156] Wignall, B.K. and Fox, A.J. Mortality of female gas mask assemblers. Br J Ind Med. 39(1):34-38, 1982.
[157] Pira, E., Romano, C., Violante, F.S., *et al.* Updated mortality study of a cohort of asbestos textile workers. Cancer medicine. 5(9):2623-28, 2016.
[158] Magnani, C., Ferrante, D., Barone-Adesi, F., *et al.* Cancer risk after cessation of asbestos exposure: A cohort study of Italian asbestos cement workers. Occup Environ Med. 65(3):164-70, 2008.
[159] Wilczynska, U., Szymczak, W. and Szeszenia-Dabrowska, N. Mortality from malignant neoplasms among workers of an asbestos processing plant in Poland: Results of prolonged observation. Int J Occup Med Environ Health. 18(4):313-26, 2005.
[160] Wang, X., Lin, S., Yu, I., *et al.* Cause-specific mortality in a Chinese chrysotile textile worker cohort. Cancer Sci. 104(2):245-49, 2013.
[161] Second Supplemental Report, William E. Longo, PhD and Mark W. Rigler, PhD, 2/1/19.

tremolite asbestos concentration associated with mesothelioma demonstrates that it is nonsensical and scientifically invalid to attribute increased mesothelioma risk to use of talcum products containing alleged asbestos.

i) Drs. Longo and Rigler's analysis

Plaintiffs' experts, Drs. William E. Longo and Mark W. Rigler, used a range of analytical methods to quantify potential asbestos in 57 Johnson's Baby Powder and Shower to Shower talcum products and 15 historical Imerys-supplied "railroad car" samples.[162] They conclude that the ATEM (analytical transmission electron microscope), coupled with the "ISO 22262-02 heavy liquid separation" method, was the most sensitive for detection of alleged asbestos fibers, as that method detected at least one alleged asbestos fiber in 42 of the 70 samples tested by ATEM. In the samples reported to be positive for asbestos fibers or bundles, concentrations ranged from 4.4 to 268 fibers-bundles/mg (or structures/mg) of talc.[163]

As noted in the human health risk assessment section (see page 9), it is necessary to know the amount a person would be exposed to (the exposure concentration) in order to assess dose and any potential risk from alleged asbestos fibers from talcum products. The following exposure estimate assumes all concentrations reported by Drs. Longo and Rigler were accurately and correctly identified as asbestiform fibers and the concentration of asbestos in the bulk talcum products remains the same in airborne talcum products. Drs. Longo and Rigler's analysis of Johnson's Baby Powder and Shower to Shower talc products reported the highest concentration was 268 structures/mg (sample M68503-026 STS, 2018-0061-08 STS 042) in a sample of Shower to Shower (the next highest sample was 95 structures/mg for a sample of Shower to Shower; sample 65D STS, 20180061-65D STS029).[164]

Based on this analysis of bulk materials, Drs. Longo and Rigler's report concludes: "*individuals who used Johnson & Johnson talcum powder products (Johnson's Baby Powder & Shower to Shower) in the past would have, more likely than not, been exposed to* ***significant*** *airborne levels of regulated amphibole asbestos* [emphasis added]."[165] However, purported asbestos fiber concentrations in bulk material alone are insufficient to determine whether there is a risk associated with talcum powder use. Their approach would be much like measuring the amount of vodka in a bottle and concluding that an individual would more likely than not have gotten drunk or had a high risk of getting drunk, without considering how much vodka an individual actually consumed.

In non-statistical terms, the word "significant" is an adjective with multiple potential definitions, including: (1) having or expressing meaning: meaningful; (2) having or expressing a covert meaning: suggestive; or (3) momentous: important.[166] Drs. Longo and Rigler use the word

[162] Second Supplemental Report, William E. Longo, PhD and Mark W. Rigler, PhD, 2/1/19.
[163] Second Supplemental Report, William E. Longo, PhD and Mark W. Rigler, PhD, 2/1/19, p. 33.
[164] Second Supplemental Report, William E. Longo, PhD and Mark W. Rigler, PhD, 2/1/19.
[165] Second Supplemental Report, William E. Longo, PhD and Mark W. Rigler, PhD, 2/1/19, p. 32.
[166] Webster's II New Riverside University Dictionary. Boston, MA: The Riverside Publishing Company. 1984.

"significant" to describe the attributed fiber exposure without explaining why it was considered meaningful or important. A scientifically-accepted way determining if their fiber exposure was "significant" would be to compare it to known exposure concentrations or recommended exposure concentrations/limits, which are concentrations considered protective of health.

Using generally-accepted scientific methods to assess risk based on Dr. Longo and Rigler's analytical results is more complicated than they report. As described in subsequent sections, we must estimate anticipated dose: first by converting the number of fibers measured in a weight of bulk material into an airborne concentration and then measuring/estimating the amount of time spent breathing that airborne concentration.

ii) Terminology

The airborne (exposure) concentration of an agent and the subsequent total dose inhaled are key parameters used to assess the potential risk for adverse health effects from that agent. As the name implies, an **airborne concentration** is the concentration of the agent in the air; the concentration can be an instantaneous measurement or an average concentration over some time period. The **dose** is the amount of agent to which a living system is exposed. For inhaled agents, the **dose** depends on the amount of time spent inhaling an **airborne concentration**.[167] For example, consider hypothetical airborne exposure concentrations of 1 and 4 structures/cc [structures/cubic centimeter; 1 cc = 1 mL]. A person would get the same inhaled dose if he or she spent four hours breathing one structures/cc or one hour breathing four structures/cc. Therefore, both airborne concentration and the time exposed are key parameters for assessing inhalation toxicology.

The term "time-weighted average" (TWA) is used to express a concentration that varies with time; it represents the average concentration, weighted for the time duration that the sample was taken.[168] The general equation for TWA calculations, where C = concentration, T = sampling time (see Equation 1).

$$\text{TWA (time T)} = \frac{C_1 \times T_1 + C_2 \times T_2 + \ldots + C_n \times T_n}{T_1 + T_2 + \ldots + T_n} \qquad \text{Equation 1}$$

iii) Converting Drs. Longo and Rigler's bulk measurements to airborne concentrations

The potential airborne dust concentrations resulting from use of talcum products was recently published in peer-reviewed literature (Anderson et al., 2016).[169] The study design incorporated multiple (five) subjects (three women and two men, self-reported as current and/or

[167] Hayes, A.W. Principles and Methods of Toxicology. 6th ed. Boca Raton: CRC Press: Taylor & Francis. 2014. p. 453-468, 488-490; Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 1553.

[168] Hayes, A.W. Principles and Methods of Toxicology. 6th ed. Boca Raton: CRC Press: Taylor & Francis. 2014. p. 682-684; Lewis, R.A. Lewis' Dictionary of Toxicology. Boca Raton: Lewis Publishers, an imprint of CRC Press LLC. 1998.

[169] Anderson, E.L., Sheehan, P.J., Kalmes, R.M. and Griffin, J.R. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. Risk Analysis. 1-12, 2016.

past talc users) and duplicate simulations for each subject. Powdering simulations occurred with subjects in a controlled chamber who were asked to apply the talcum powder product "*as they typically would after a bath or shower*." Each simulation lasted 48 minutes, during which time each participant was asked to apply powder eight separate times, with approximately 6-minute intervals between applications. The resulting average respirable dust concentrations for the 48-minute simulation encompassing eight powdering events ranged from 0.26 to 5.03 mg talc/m^3.[170] These results are consistent with an earlier, preliminary study that reported a five-minute maximum respirable talc concentration of 3.3 mg talc/m^3 (simulated with four female subjects performing duplicate assessments of adult dusting powder); average values were 1.13 mg/m^3 and 1.9 mg/m^3 [for] 32 non-micronized and eight micronized five-minute talc simulations, respectively.[171]

A different peer-reviewed publication by Gordon et al. (2014) that investigated airborne fiber exposure concentration following application of talc was not included in this assessment (total airborne concentrations of talc were not reported).[172] The investigators used talcum powders containing 67 to 260-times more asbestos fibers than the highest concentration reported by Drs. Longo and Rigler (above) and resulting airborne concentrations of each talc were assessed with a single experiment (N=1) where talc was applied using a "shaker container" or a "puff applicator" by a male applicator with unknown prior talcum use history. The study design (i.e., single sampling events by a single male investigator) was of unknown relevance to a woman's perineal application of talc, had unknown experimental variability and accuracy, and therefore was not included in the discussion below.

The maximum bulk concentration of amphibole asbestos structures per milligram of talcum product reported by Drs. Longo and Rigler (268 structures/mg talc; see above) can be converted to an estimated airborne concentration using the conservative assumption that the maximum average concentration measured by Anderson et al. (2016, detailed above) over 48 minutes and eight powdering events (5.03 mg talc/m^3) was attained for six minutes daily for a talcum product user. The worst-case average airborne concentration of asbestos calculated with the **highest concentration of structures found in talc and the highest measured concentration by users over the six-minute exposure was 0.001348 structures/cc** (see Equation 2).

$$\text{Airborne asbestos (6-minute duration)} = \frac{5.03 \text{ mg talc}}{\text{m}^3 \text{ air}} \times \frac{268 \text{ structures}}{1 \text{ mg talc}} \times \frac{1 \text{ m}^3 \text{ air}}{1{,}000{,}000 \text{ cc air}} \qquad \text{Equation 2}$$

$$\text{Airborne asbestos (6-minute duration)} = 0.001348 \text{ structures/cc}$$

[170] Anderson, E.L., Sheehan, P.J., Kalmes, R.M. and Griffin, J.R. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. Risk Analysis. 1-12, 2016.
[171] Aylott, R.I., Byrne, G.A., Middleton, J.D. and Roberts, M.E. Normal use levels of respirable cosmetic talc: preliminary study. Int J Cosmet Sci. 1(3):177-86, 1979.
[172] Gordon, R.E., Fitzgerald, S. and Millette, J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. Int J Occup Environ Health. 20(4):318-32, 2014.

iv) Comparing Drs. Longo and Rigler's results to known acceptable levels

The following discussion compares the airborne concentrations resulting from the powdering simulation studies described above to: (1) the lowest concentration associated with mesothelioma in occupational workers; and (2) workplace exposure limits.

Recommended occupational concentrations, summarized in Table 8, are the concentrations considered protective of worker safety and health, when exposed over a working lifetime.

Table 8. Asbestos recommended workplace exposure limits

Agency	Exposure Limit	Value (structures/cc)	Averaging duration
OSHA[173]	Personal exposure limit (PEL)	0.1	8 hr TWA
NIOSH[174]	Recommended exposure limit (REL)	0.1 (prefer lowest feasible concentration)	8 hr TWA
ACGIH[175]	Threshold limit value (TLV)	0.1	8 hr TWA
CAL OSHA[176]	Personal exposure limit (PEL)	0.1	8 hr TWA

Cumulative asbestos exposure over a working lifetime (in units of structures/cc-year) is the average eight-hour TWA concentration per year (assuming occupational exposure 250 days per year) times the number of years of the working environment. When combined with a 50-year work history, the **eight-hour OSHA PEL of 0.1 structures/cc corresponds to a lifetime cumulative exposure of five structures/cc-year**.

A similar calculation can convert the worst-case lifetime airborne asbestos concentration associated with daily use of talcum products (0.001348 structures/cc, calculated in Equation 2) assuming the duration of talc use is six minutes (0.1 hr) per day, applied every day of the year, over 50 years. In order to compare the numbers, the concentration from talcum products must be converted from a six-minute TWA into an eight-hour TWA and the use characteristics updated to reflect use of the product every day of the year (instead of the 250 assumed working days assumed in the occupational exposure). From the calculations described in Equation 3, the worst-case, upper bounds lifetime cumulative **asbestos exposure from using talc daily for 50 years is 0.0012 structures/cc-year**.

[173] OSHA. 29 CFR Parts 1910, 1915, and 1926 Occupational exposure to asbestos; Final rule. Federal Register. 59(153):40964-1162, 1994.
[174] NIOSH. Criteria for a Recommended Standard: Revised Recommended Asbestos Standard. December, 1976.
[175] ACGIH. Asbestos, All Forms. In: Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH 2001.
[176] California Code of Regulations. Subchapter 7. Group 16. Article 110. Section 5208.

Cumulative asbestos exposure using Longo and Rigler's worst-case talc product = 0.001348 structures/cc X $\frac{0.1 \text{ hr}}{8 \text{ hr}}$ X $\frac{365 \text{ days}}{250 \text{ days}}$ X 50 years Equation 3

= 0.0012 structures/cc-year (over 50 years of exposure)

The lifetime asbestos concentration associated with OSHA's PEL (for which no increased risk of mesothelioma has been demonstrated) is more than 4,000 times more than the worst-case lifetime airborne asbestos concentration associated with daily use of talcum products (see Table 9).

A relevant comparison for the lifetime exposure associated with the maximum concentration of asbestos reported by Drs. Longo and Rigler would be to the exposure associated with the average background ambient airborne asbestos concentrations in the United States. A recent review compiled historical data for the decades from the 1960s to the 2000s.[177] Concentrations generally decreased with progressive decades; the lowest average (0.000017 structures/cc from the 2000s) was selected as the most conservative value for comparison. A similar conversion to that described above was used to convert the concentration into an everyday of the year exposure, breathed 24 hours/day. Fifty years of exposure to background, ambient levels corresponds to a lifetime, cumulative asbestos concentration of 0.0037 structures/cc-year, which is more than three times more than the worst-case lifetime airborne asbestos concentration associated with daily use of talcum products (see Table 9).

Another metric for comparison is the lowest observed concentration associated with mesothelioma (lowest-observable-adverse-effect level), which was estimated following an extensive analysis of the relationship between mesothelioma incidence in workers occupationally exposed to tremolite asbestos at the Thetford mines and the Libby vermiculite deposits. The estimated value for the lowest fiber/cc-year concentration associated with mesothelioma was between 35 and 73 f/cc-year,[178] which was more than 29,000 to 60,000 times above the worst-case, upper bounds lifetime cumulative asbestos exposure from using talc daily for 50 years (see Table 9).

[177] Abelmann, A., Glynn, M.E., Pierce, J.S., *et al.* Historical ambient airborne asbestos concentrations in the United States – an analysis of published and unpublished literature (1960s-2000s). Inhal Toxicol. 27(14):754-66, 2015.
[178] Finley, B.L., Pierce, J.S., Phelka, A.D., *et al.* Evaluation of tremolite asbestos exposures associated with the use of commercial products. Crit Rev Toxicol. 42(2):119-46, 2012.

Table 9. Cumulative lifetime estimated asbestos concentrations

Description	Concen-tration structures /cc	Sample duration	8-hr TWA, structures /cc	Conversion factor (exposure days)	Conversion factor (continuous exposure)	50-year Cumulative exposure (structure/ cc-years)	Ratio to max talc[B]
Longo and Rigler talcum powder analysis maximum value[179]	0.001348[A]	6 min	0.00001685	365 days/ 250 days	n/a	0.0012	1.0
Ambient asbestos concentration in the US in the 2000s[180]	0.000017	Annual average	0.000017	365 days/ 250 days	24 hours/ 8 hours	0.0037	3.1
OSHA PEL[181]	0.1	8 hour	0.1	n/a	n/a	5.0	4,170
Lowest cumulative tremolite asbestos concentration associated with mesothelioma[182]	-	-	-	-	-	35.0	29,200

[A] See text for derivation (performed using structures/mg talc reported by Longo and Rigler with six-minute airborne concentration of talc measured for powdering events by Anderson et al. (2016))[183]
[B] Ratio of the respective 50-year cumulative exposure concentration to the 50-year cumulative exposure concentration of the Longo and Rigler talcum powder analysis maximum value

If indeed talcum products contained asbestos fibers, concentrations were not significant (as alleged by Drs. Longo or Rigler)[184] or meaningful compared to lifetime ambient exposure levels, allowable workplace exposure levels and the lowest cumulative tremolite asbestos concentration associated with mesothelioma.

e. Assessment

Studies of humans occupationally exposed have observed some studies with statistically significant effects toward ovarian cancer, although those effects are less compared to the exposure's effect on mesothelioma (as described earlier in this report, see discussion beginning

[179] As derived perviously in ths report using the maximum amount of structures observed in any bulk talc sample analyzed in the Second Supplemental Report, William E. Longo, PhD and Mark W. Rigler, PhD, 2/1/19.
[180] Abelmann, A., Glynn, M.E., Pierce, J.S., *et al.* Historical ambient airborne asbestos concentrations in the United States – an analysis of published and unpublished literature (1960s-2000s). Inhal Toxicol. 27(14):754-66, 2015.
[181] OSHA. 29 CFR Parts 1910, 1915, and 1926 Occupational exposure to asbestos; Final rule. Federal Register. 59(153):40964-1162, 1994.
[182] Finley, B.L., Pierce, J.S., Phelka, A.D., *et al.* Evaluation of tremolite asbestos exposures associated with the use of commercial products. Crit Rev Toxicol. 42(2):119-46, 2012.
[183] Anderson, E.L., Sheehan, P.J., Kalmes, R.M. and Griffin, J.R. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. Risk Analysis. 1-12, 2016.
[184] Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD, 11/14/18, p. 26.

on page 40). It follows, then, that if ovarian cancer is associated with asbestos exposure, levels that are not associated with mesothelioma will also not cause ovarian cancer.

Assessment of Drs. Longo and Rigler's exposure concentration associated with powdering using the highest asbestos-burdened talc found, using conservative assumptions of all other factors (use, frequency, duration), still results in 50-year cumulative airborne asbestos fiber exposures that are three times below those associated with ambient, background exposure; at least 4,000 times below those derived working for 50 years at the OSHA PEL; and at least 29,000 times below tremolite asbestos levels considered protective of mesothelioma.

This analysis supports the conclusion that scientific studies do not show that asbestos, as an alleged contaminant in talc, causes ovarian cancer in women.

2. Chromium

a. Key opinions

- No association has been found between chromium and ovarian cancer in humans or animals.
- Carcinogenic propensity of chromium is very different depending on the valence state (i.e., charge) of the chromium ion considered. Chromium(III), commonly found in rocks, is not associated with cancer. Chromium(VI), the formation of which is associated with industrial processes, has been shown to be a carcinogen with high occupational exposures of airborne chromium(VI) associated with increased risk of respiratory (lung) cancer (but not dermal).
- There are no scientific data supporting the concept that alleged trace levels of chromium in talc products cause ovarian cancer.

b. Overview

Chromium exists mainly as chromium(III) (also known as trivalent chromium) and chromium(VI) (also known as hexavalent chromium). Chromium(III) is the more stable ionic state and chromium(VI) is reduced by reducing agents or oxidizable organic matter to chromium(III).[185]

Chromium(III) is a naturally-occurring trace nutrient. Scientific evidence suggests it may serve as a cofactor for insulin in glucose metabolism, but the specific biomolecules and mode of action have not been established. Regardless, chromium(III) remains a top-selling nutritional supplement with doses that typically range from 50 to 200 µg [per day] of chromium(III).[186] There are no demonstrated toxic effects of consuming high levels of supplemented

[185] IARC. Chromium (VI) Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012.
[186] US DHHS. Chromium. Dietary Supplement Fact Sheet. Last updated September 21, 2018. Available from: https://ods.od.nih.gov/factsheets/chromium-Health%20Professional/#h10. Accessed: February 19, 2019.

chromium(III).[187] The Institute of Medicine of the National Research Council established an adequate intake level (the amount assumed to be adequate for health) of 21-35 µg/day for adolescents and adults.[188]

c. Exposure sources

Chromium is found in rocks, animals, plants and soils, where it exists in combination with other elements to form various compounds. Non-occupational human exposure most often occurs through ingestion of trace levels in foods and occasionally though drinking chromium-containing ground water. Inhalation exposure can also occur if chromium is released into the air, which may occur from industries using or manufacturing chromium, by living near a chromium-containing hazardous waste facility or through cigarette smoke.[189]

Chromium(III) is the most stable oxidation state and is the form of chromium in the food supply.[190]

Some individuals consume chromium dietary supplements. Estimates from 1986 indicated 8% of adults consumed chromium[(III)]-containing supplements; according to the Third National Health and Nutrition Examination Survey data the median supplemental intake was 23 µg/day and intakes at the 95th percentile were 100 and 127 µg/day for men and women, respectively.[191] The UK Expert Group on Vitamins and Minerals (EGVM) reported daily intake from supplements can be up to 600 µg/day,[192] and a European Food Safety Authority (EFSA) panel estimated the combined intake from fortified foods, foodstuffs, and supplements to be about 910 and 1,540 µg/day for typical and 95th-percentile intake levels, respectively.[193] The Institute of Medicine (IOM; now the National Academy of Medicine; NAM) did not recommend an upper exposure limit due to the lack of serious adverse effects associated with excess dietary intake of chromium(III).[191] No dietary intake or background exposure levels specific for chromium(VI) were located.

Chromium(VI) is rarely found in nature. It is formed as a by-product of industrial processes (e.g., manufacturing stainless steel, pigments, chromate chemicals and numerous other

[187] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 1139; Vincent, J.B. Chromium: is it essential, pharmacologically relevant, or toxic? Met Ions Life Sci. 13:171-98, 2013.
[188] Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2001.
[189] ATSDR. Toxicological Profile for Chromium. Atlanta, Georgia. September, 2012.
[190] Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2001.
[191] Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2001.
[192] Expert Group on Vitamins and Minerals (EGVM). Safe Upper Levels for Vitamins and Minerals. May, 2003.
[193] EFSA Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on the risks to public health related to the presence of chromium in food and drinking water. EFSA Journal. 12(3):3595, 2014.

products).[194] Chromium(VI) is also used as a pigment in dyes, paints, inks and plastics, or as an anti-corrosive in paints and other coatings.[195] Chromium(VI) is strongly oxidizing.[191]

d. Current exposure guidelines and standards

Different scientific and regulatory bodies have derived chromium exposure concentrations to which a person can be exposed over a lifetime without any adverse health impact:

- **Chromium(III):** The US FDA and the ICH determined the permitted daily exposure levels (PDEs) without risk of adverse health impact for chromium(III) in adults via oral, parenteral [injection], and inhalation exposure routes to be 10,700, 1,070, and 2.9 µg/day, respectively.[196]
- **Chromium(VI):** The US FDA and ICH did not derive PDEs for chromium(VI) because chromium intake from pharmaceuticals would consist of only chromium(III) unless chromium(VI) was used as a catalyst.[197]
- **Chromium (all valence states):** The allowable level in bottled drinking water in the United States is 100 µg/L total chromium (i.e., the sum of all valence states).[198] Assuming a person drinks 2 L/day, this corresponds to an acceptable total intake of 200 µg/day total chromium.

The US EPA used lung cancer incidence from inhalation exposures in workers and a linear dose-response model to derive a unit risk estimate of 0.012 for exposure to air containing 1 µg (0.001 mg) chromium(VI)/m^3.[199]

e. Animal carcinogenicity studies

There are no animal studies showing that chromium is associated with an increased risk of ovarian cancer.

Chromium(III): Animal carcinogenicity studies for chromium(III) are limited and do not provide support for claims of carcinogenicity.[200] IARC determined there was *inadequate evidence* in experimental animals for the carcinogenicity of chromium(III).[201]

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[194] Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2001; McEwen, G. Re: Call for Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition (69 Federal Register 28940): Cosmetic Talc. In: Jameson, C.W., editor. 2004., p. 1122.

[195] North Carolina Department of Labor. A Guide to Hexavalent Chromium Cr(VI) for Industry. 2013. Available at: http://www.nclabor.com/osha/etta/indguide/ig45.pdf.

[196] ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014; US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015.

[197] ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014; US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015.

[198] FDA. CFR Title 21 Food and Drugs; Part 165 - Beverages. Section 165.110 Bottled water. Code of Federal Regulations. 2016.

[199] US EPA. Chromium (VI); CASRN 18540-29-9. Sept 3, 1998.

[200] ATSDR. Toxicological Profile for Chromium. Atlanta, Georgia. September, 2012.

Chromium(VI): Chronic studies provide evidence that chromium(VI) is a pulmonary carcinogen via inhalation and gastrointestinal tract carcinogen via oral exposures in animals. IARC determined there was *sufficient evidence* in experimental animals for the carcinogenicity of chromium(VI) compounds.[202] Specifically:

- Inhalation exposures are associated with increased respiratory tract tumors. Increased lung tumor incidence was observed with exposures of 4.3 mg/m^3 in mice compared with controls and other respiratory-tract exposure studies (via intratracheal, intrapleural, and intrabronchial) observed respiratory tract tumors. No carcinogenic effects were observed in rats, rabbits or guinea pigs exposed to a lesser concentration (1.6 mg/m^3).[203]
- Ingestion (via drinking water) resulted in cancers of the gastrointestinal tract of rodents; the most sensitive effects occurred in mice exposed to 2.4 mg chromium(VI)/kg/day.[204]

f. Human cancer studies and conclusions

No human studies have reported a relationship between chromium (of any valance state) and ovarian cancer. No regulatory body or scientific organization has concluded a causal relationship between chromium and ovarian cancer exists.

Potential risk for chromium toxicity is related to the valence state of the chromium to which one is exposed (e.g., III vs. VI).

There is a consensus in the scientific community that there are no known adverse effects associated with exposure to chromium(III). Studies for each chromium valence state are reviewed below as follows:

- **Chromium(III):** Limited epidemiology studies are available for chromium(III). IARC determined there was *inadequate evidence* in humans for carcinogenicity of chromium(III).[205]
- **Chromium(VI):** Occupational exposure to chromium(VI) compounds has been associated with increased risk of respiratory system cancers.[206] Chromium(VI) compounds were classified by IARC (2012) as Group 1 human carcinogens with *sufficient evidence* of carcinogenicity in humans and animals. IARC concluded epidemiology data was sufficient to show that inhalation exposure to chromium(VI) increases the risk of lung cancer; the relative risks were highest for chromate production workers (where exposures were greatest) and lesser for workers in other industries, who may had have had somewhat lower levels of exposure. Epidemiological evidence was

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[201] IARC. Chromium (VI) Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 147-67.
[202] IARC. Chromium (VI) Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 147-67.
[203] ATSDR. Toxicological Profile for Chromium. Atlanta, Georgia. September, 2012.
[204] ATSDR. Toxicological Profile for Chromium. Atlanta, Georgia. September, 2012.
[205] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 49. Chromium and Chromium Compounds. In:Chromium, Nickel, and Welding. Lyon, France: World Health Organization International Agency for Research on Cancer; 1990. p. 49-256.
[206] ATSDR. Toxicological Profile for Chromium. Atlanta, Georgia. September, 2012.

inconclusive for associations with either nose and nasal sinus cancer or stomach cancer. There was no indication chromium(VI) elicited any dermal effects or was associated with any type of cancer beyond effects to the respiratory system.[207]

g. Alleged levels in talc

There are no scientific data supporting the concept that alleged trace levels of chromium in talc products cause ovarian cancer.

Transport, solubility, absorption and excretion of metals in talc within the body is unknown. Quantity (dose, if any) from alleged trace metals in talc to the ovarian tissue is unknown.

Despite these vast scientific uncertainties regarding dose, there is one fundamental scientific principle that contradicts claims that alleged chromium levels as a contaminant in talc are a causative factor for ovarian (or any) cancer. Carcinogenicity of chromium depends on the valence state (i.e., charge) of the chromium compound (III or VI). Chromium(III), commonly found in rocks, is not associated with cancer,[208] and, if chromium is present in talc products, it is most likely in the form of chromium(III) present in rock. This assumption is supported by the single analysis identified that was specific for chromium(VI), which reported talc (unclear if it was bulk ore or final talcum product) contained <0.1 ppm Cr(VI) (no analysis was performed for Cr(III)).[209]

Scientific data do not support the concept that the levels of chromium in talc products cause ovarian cancer.

h. Critique of chromium evaluation by plaintiffs' experts

Plaintiffs' experts use hazard identification statements (e.g., IARC-assigned human carcinogenicity categorizations) to identify potential hazards (cancer)[210] that they allege may be associated with perineal application of talc. However, relying on a hazard identification statement (assigned based on carcinogenicity to non-ovarian tissues), without considering the exposure levels necessary for the potential hazard (e.g., chromium(VI) in talc) to pose a specific risk of human ovarian cancer is not consistent with the established methods toxicologists use to conduct risk assessment (see page 9, above).

Plaintiffs' experts fail to address that the potential carcinogenicity varies with the valence state of the chromium compound under consideration. As described above, the carcinogenic

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[207] IARC. Chromium (VI) Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 147-67.
[208] ATSDR. Toxicological Profile for Chromium. Atlanta, Georgia. September, 2012.
[209] Talc analyses of talc products report total chromium (and do not speciate between III and VI). The one analysis identifed specific for VI reported <0.1 ppm CrVI, but it was unclear if this was bulk ore or final talcum product supplied to consumers. Corresponding level for CrIII was not reported (JNJ000378044, JNJ000378046).
[210] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8; Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Rebecca Smith-Bindman, MD, 11/15/18, p. 5, 16; Expert Report of Mark Krekeler, PhD, 11/16/18, p. 6-7; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.

potential of chromium depends upon its valence state, with carcinogenicity associated with exposure to chromium(VI) but not with exposure to chromium(III).

- Analyses by plaintiffs' experts Drs. Carson, Plunkett and Cook failed to acknowledge that different forms of chromium exist.[211] Scientific knowledge clearly shows there are different toxicities for chromium depending on the valence state to which one is exposed. Apparent omission of this critical information (e.g., the carcinogenicity of chromium depends on its valence state) is inconsistent with the comprehensive data review performed by toxicologists as part of the human health risk assessment process.
- Analyses by plaintiffs' experts Drs. Carson, Plunkett, Smith-Bindman and Cook indicate their concern was for chromium (no valence state) in talc products.[212] Failure to consider the valence state of chromium associated with talc before drawing conclusions regarding carcinogenicity is methodologically invalid and not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.
- It was unclear from Dr. Zelikoff's report whether she reviewed documents that had reported chromium(VI) in the talc products at issue.[213] Dr. Krekeler's analysis acknowledged the absence of testing to determine the valence states of the chromium detected in talc.[214] Without the specific knowledge of chromium(VI) concentrations within talc products, any conclusions regarding the potential carcinogenicity of chromium (no valence state) are not scientifically valid.

Plaintiffs presuppose chromium (no valence state) in talc products is a hazard, but fail to acknowledge that human exposure to chromium(III) (and to a lesser extent chromium(VI)) is ubiquitous. As described above, people ingest trace levels in foods and drinking water and may take chromium(III) as part of a dietary supplement.[215]

When asked about how much nickel, cobalt and chromium reached the ovary with a single application of Johnson's Baby Powder to the perineum, Dr. Zelikoff testified that this "*information is not available*."[216] This response implies she has not made any consideration relating to the dose of chromium potentially involved in such a process. Her testimony that an effect can be claimed without regard to dose is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

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[211] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.
[212] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 18, 24, 46, 67-69, 77; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-8; Expert Report of Rebecca Smith-Bindman, MD, 11/15/18, p. 5; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.
[213] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 11.
[214] Expert Report of Mark Krekeler, PhD, 11/16/18, p. 36.
[215] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8; Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Rebecca Smith-Bindman, MD, 11/15/18, p. 5, 16; Expert Report of Mark Krekeler, PhD, 11/16/18, p. 6-7; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.
[216] Deposition of Judith Zelikoff, PhD, 1/21/19, 288:10-15.

When asked about the exposure level needed to have biologic plausibility with ovarian cancer, Dr. Zelikoff testified that these metals (cobalt, chromium and nickel) have the ability to produce inflammation at "*very, very low levels. And if they produce inflammation, then they have the potential to go on to cancer. And many of these metals do*."[217] Her testimony that an effect can be claimed without regard to dose is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

Dr. Zelikoff testified that one particle of chromium(VI), either inhaled or applied to the perineum, could induce inflammation in the ovaries.[218] Scientifically, the one-particle statement is as speculative as it is unverifiable. Her testimony that an effect can be claimed without regard to dose is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

3. Cobalt

a. Key opinions

- No association has been found between cobalt and ovarian cancer in humans or animals.
- The allegation that a trace level of cobalt can cause ovarian cancer is not consistent with established scientific knowledge. Cobalt is an essential metal, and its intake is required for human health.
- There are no scientific data supporting the concept that alleged trace levels of cobalt cause ovarian cancer.

b. Overview

Cobalt (Co) is a naturally-occurring, ubiquitous compound present in several different forms. The most common oxidation states are cobaltous (Co2+) and cobaltic (Co3+), the former being most commercially and environmentally available.[219] Cobalt is an essential metal as a metal cofactor coordinated in vitamin B_{12}, which is required for the production of red blood cells.[220]

c. Exposure sources

Cobalt is a naturally-occurring element that is widely dispersed in the environment in low concentrations.[221] Diet constitutes the main route of exposure for humans. Cobalt is an essential component of Vitamin B_{12}, which is, in turn, essential to human health.[222] Cobalt in the

[217] Deposition of Judith Zelikoff, PhD, 1/21/19, 282:19-24.
[218] Deposition of Judith Zelikoff, PhD, 1/21/19, 321:21-322:5, 322:16-21.
[219] Leyssens, L., Vinck, B., Van Der Straeten, C., Wuyts, F. and Maes, L. Cobalt toxicity in humans—A review of the potential sources and systemic health effects. Toxicology. 387:43-56, 2017.
[220] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 1131.
[221] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.
[222] De Boeck, M., Kirsch-Volders, M. and Lison, D. Cobalt and antimony: genotoxicity and carcinogenicity. Mutat Res. 533(1-2):135-52, 2003; ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.

environment may also result from human activities; higher levels may be found in proximity to vehicular exhaust or other sources of industrial pollution.[223]

Insoluble cobalt is often used in combination with other metals to form corrosion- and wear-resistant alloys. Such alloys are used in aircraft engines, magnets, steels, cutting and grinding tools, as well as in artificial hip replacements and knee joints.[224] Cobalt compounds have other applications in electroplating and electrochemical industries, in batteries, as coloring agents (e.g., ceramics, glass), as a drying agent (e.g., inks, paints, varnishes and linoleum), as catalysts for the petroleum and chemical industries, and in medical applications (historical treatment of anemia, various joint prostheses).[225] Cobalt can also exist in radioactive forms (^{60}Co or ^{58}Co), which are used for medical and scientific research purposes.[226]

For most people, the largest source of cobalt intake is inorganic cobalt in food (vitamin B_{12} constitutes only a very small fraction of total cobalt intake).[227] Occupational exposures exceeding environmental and dietary exposures may occur for those using cobalt in industrial settings, such as metal mining, smelting, refining, during manufacture, maintenance, or use of cutting or grinding tools, or in other hard-metal industries producing or using cobalt.[228] Occupational exposures result mainly from breathing cobalt-containing dust,[229] though dermal exposures may occur in some settings.[230]

d. Current exposure guidelines and standards

The recommended dietary allowance of vitamin B_{12} is 2.4 µg/day, which contains 0.1 µg of cobalt.[231] The Expert Group on Vitamins and Minerals reported the daily exposure estimate for cobalt from food averaged 12 µg/day.[232]

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[223] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.
[224] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004; IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 86. Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France. 2006; Christian, W.V., Oliver, L.D., Paustenbach, D.J., Kreider, M.L. and Finley, B.L. Toxicology-based cancer causation analysis of CoCr-containing hip implants: a quantitative assessment of genotoxicity and tumorigenicity studies. J Appl Toxicol. 34(9):939-67, 2014.
[225] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004; IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 86. Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France. 2006; Leyssens, L., Vinck, B., Van Der Straeten, C., Wuyts, F. and Maes, L. Cobalt toxicity in humans—A review of the potential sources and systemic health effects. Toxicology. 387:43-56, 2017.
[226] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.
[227] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.
[228] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004; IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 86. Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France. 2006.
[229] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.
[230] Klasson, M., Lindberg, M., Bryngelsson, I.L., *et al.* Biological monitoring of dermal and air exposure to cobalt at a Swedish hard metal production plant: does dermal exposure contribute to uptake? Contact Dermatitis. 77(4):201-07, 2017.
[231] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004.
[232] Expert Group on Vitamins and Minerals (EGVM). Safe Upper Levels for Vitamins and Minerals. May, 2003.

The US FDA and ICH have established permitted daily exposure levels (for cobalt as a trace constituent in pharmaceuticals) without risk of adverse health impact via oral, parenteral [injection] and inhalation exposure routes of 50, 5.0, and 2.9 µg/day, respectively.[233]

ATSDR and the World Health Organization derived a minimum risk level (MRL) of 0.1 $\mu g/m^3$ for chronic inhalation of cobalt based on non-cancer effects observed in higher exposed workers (i.e., spirometry effects observed with exposure to 15.1 $\mu g/m^3$).[234]

e. Animal carcinogenicity studies

There are no animal studies showing cobalt is associated with an increased risk of ovarian cancer despite the wide variety of animal toxicology studies that have been performed.

Chronic toxicity studies of a cobalt sulfate and of cobalt metal – which are both 100% bioaccessible, meaning they dissolve to release cobalt ions – were conducted by the National Toxicology Program on both rats and mice of both sexes. As summarized below, no increased incidence of tumors was observed in the ovaries of treated females by either type of cobalt test article.

- **Cobalt sulfate** (inhalation, two years, rats and mice): The two-year inhalation study of cobalt sulfate at levels of 0.3, 1, or 3 mg/m^3, 6 hr/day, 5 d/week, observed increased incidence of respiratory tumors in both sexes of rats and mice, and potentially an induction of adrenal medulla pheochromocytomas in rats with marginal and increased incidence observed in treated males and females, respectively. In both mice and rats, exposure to cobalt did not cause an increased incidence of neoplasms in other tissues, including the ovaries.[235]

- **Cobalt metal** (inhalation, two years, rats and mice): The two-year inhalation study of cobalt metal at levels of 1.25, 2.5, 5 mg/m^3, 6 hr/day, 5 d/week, observed increased incidences of non-neoplastic lesions of the lung and nose in male and female rats; the testes in male rats and mice; the adrenal medulla in female rats, and the lung, nose, larynx and trachea in male and female mice. No increased incidence in neoplasms was observed in the ovaries.[236]

[233] US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015; ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014.
[234] ATSDR. Toxicological profile for Cobalt. Atlanta, GA. April, 2004; International Programme on Chemical Safety (IPCS). Cobalt and inorganic cobalt compounds. Concise International Chemical Assessment Document 69. Geneva. WHO, 2006.
[235] NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate (CAS No. 10026-24-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program technical report series. 471:1-268, 1998.
[236] NTP. NTP Technical Report on the Toxicology Studies of Cobalt Metal (CAS no. 7440-48-4) in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Cobalt Metal in F344/NTac Rats and B6C3F1/N Mice (Inhalation Studies). Research Triangle Park, NC. NTP, National Toxicology Program technical report series. Report No.: NTP TR 581. Dec, 2014.

- **Cobalt metal implantations** of 60-100 mg for 12 months resulted in pre-neoplastic lesions (but no cancer) in rats; cobalt nanoparticles were associated with increased tumors associated with the site of injection.[237]

In its 2006 evaluation, IARC reviewed a variety of inhalation, injection (intramuscular, intrathoracic, intraperitoneal, and intraosseous), implantation, and/or intratracheal instillation animal studies, but concluded that interpretation of these studies for carcinogenic evidence was difficult due to a lack of detail on statistical analyses, survival, control groups and fatality due to neoplasms. Interpretation of injection studies for carcinogenic potential of cobalt was limited because the general injection of inert foreign materials (intramuscularly or subcutaneously) is known to result in malignant tumors at the injection site in rats.[238]

f. Human cancer studies and conclusions

No human studies have observed a relationship between exposure to cobalt and ovarian cancer. No regulatory body or scientific organization has concluded that a causal relationship exists between cobalt and any type of cancer in humans.

No increased risk of ovarian cancer was observed in two occupationally exposed groups. Cohorts included porcelain plate painters who had used dyes containing approximately 25% cobalt (as an insoluble cobalt-aluminum spinel dye and a soluble cobalt silicate dye)[239] and workers from eight US hard-metal plants who had been exposed occupationally to median cobalt levels of 0.003 to 0.022 mg/m^3.[240]

Cobalt-containing alloys have been used for decades as replacement joints (e.g., hips and knees), and it is understood that these implants release metals into the bloodstream through a combination of corrosion and wear.[241] These surgical implants are known to result in exposures associated with release of cobalt particles and ions. [242] However, epidemiology reviews associated with these implants indicate no increased risk of systemic cancer for this patient population and no increase in ovarian cancer.[243]

Following an extensive review, the 2016 National Toxicology Program (NTP) cancer evaluation on cobalt concluded that "*the data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure to cobalt ...because (1) it was not*

[237] Hansen, T., Clermont, G., Alves, A., *et al.* Biological tolerance of different materials in bulk and nanoparticulate form in a rat model: sarcoma development by nanoparticles. J R Soc Interface. 3(11):767-75, 2006.
[238] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 86. Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France. 2006.
[239] Tuchsen, F., Jensen, M.V., Villadsen, E. and Lynge, E. Incidence of lung cancer among cobalt-exposed women. Scandinavian journal of work, environment & health. 22(6): 444-50, 1996.
[240] Marsh, G.M., Buchanich, J.M., Zimmerman, S., *et al.* Mortality among hardmetal production workers: US cohort and nested case-control studies. J Occup Environ Med. 59(12):e306-e26, 2017.
[241] Paustenbach, D.J., Tvermoes, B.E., Unice, K.M., Finley, B.L. and Kerger, B.D. A review of the health hazards posed by cobalt. Crit Rev Toxicol. 43(4):316-62, 2013.
[242] Leyssens, L., Vinck, B., Van Der Straeten, C., Wuyts, F. and Maes, L. Cobalt toxicity in humans—A review of the potential sources and systemic health effects. Toxicology. 387:43-56, 2017.
[243] Paavolainen, P., Pukkala, E., Pulkkinen, P. and Visuri, T. Cancer incidence in Finnish hip replacement patients from 1980 to 1995: a nationwide cohort study involving 31,651 patients. J Arthroplasty. 14(3):272-80, 1999.

possible to rule out confounding by carcinogenic co-exposures; or (2) other complications prevented a clear interpretation of a cobalt effect."[244]

IARC took a different approach in evaluating the potential carcinogenicity of cobalt in humans, as it provided different classification conclusions for the different evaluated cobalt compounds.[245] Importantly, IARC concluded that the scientific dataset was insufficient for an affirmative, causal relationship (i.e., Group 1 classification) for any type of cobalt compound with any type of human cancer. Furthermore, its strongest conclusion, which applied to cobalt metal with tungsten carbide (Group 2A), does not apply to cobalt in talc because, according to the records I reviewed, tungsten carbide is not an ingredient or contaminant of talc. IARC classifications for cobalt are:

- **Cobalt metal without tungsten carbide**: *Possibly* carcinogenic to humans (Group 2B).
- **Cobalt sulfate and other soluble cobalt(II) salts:** *Possibly* carcinogenic to humans (Group 2B)
- **Cobalt metal with tungsten carbide**: *Probably* carcinogenic to humans (Group 2A)

None of the information above has associated cobalt (in any form) with ovarian cancer in humans or animals.

g. Alleged levels in talc

There are no scientific data supporting the concept that alleged presence of trace levels of cobalt in talc products causes ovarian cancer.

Transport, solubility, absorption, and excretion of cobalt in talc within the body is unknown. Quantity (dose, if any) from alleged trace cobalt in talc to the ovarian tissue is unknown.

The allegation that a trace level of cobalt can cause ovarian cancer is not consistent with established scientific knowledge. Cobalt, an essential metal that all humans are exposed to daily, is necessary for human health. The US FDA and ICH have established permissible levels for cobalt to exist as an elemental impurity in pharmaceutical products; this daily concentration is, by definition, protective of public health for all patient populations.[246]

Scientific data do not support the concept that cobalt levels alleged to be in talc products cause ovarian cancer.

[244] NTP. Report on Carcinogens Monograph on Cobalt and Cobalt Compounds That Release Cobalt Ions In Vivo. Research Triangle Park, NC. Report No.: NIH# 16-5987. April 22, 2016.
[245] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 86. Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France. 2006.
[246] US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015; ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014.

h. Critique of cobalt evaluation by plaintiffs' experts

Plaintiffs' experts use hazard identification statements (e.g., IARC-assigned human carcinogenicity categorizations) to identify potential hazards (cancer)[247] they allege may be associated with perineal application of talc. However, relying on a hazard identification statement (assigned based on carcinogenicity to non-ovarian tissues), without considering the exposure levels necessary for the potential hazard (e.g., cobalt in talc) to pose a specific risk of human ovarian cancer, is not consistent with the established methods toxicologists use to conduct risk assessment (see previous report section regarding human health risk assessment, page 9).

Claiming that cobalt can cause ovarian cancer without acknowledging the role of dose and failing to characterize the dose needed to see an effect is not generally accepted by the scientific community. Most plaintiffs' experts presuppose that cobalt in talc products is a hazard, but fail to acknowledge that human exposure to cobalt is ubiquitous and necessary.[248] When asked what dose was required (of the whole talcum product) to start the biological process of talc and ovarian cancer, Dr. Zelikoff testified "*It's unknown, it's not in the literature*."[249] Her testimony that an effect can be claimed without regard to dose is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

As noted above, when asked about how much nickel, cobalt and chromium reached the ovary with a single application of Johnson's Baby Powder to the perineum, Dr. Zelikoff testified that this "*information is not available*."[250] This response implies she has not made any consideration relating to dose of cobalt potentially involved in such a process, thereby claiming an effect without regard to dose, which is inconsistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

Dr. Zelikoff testified that these metals (cobalt, chromium and nickel) have the ability to produce inflammation at "*very, very low levels. And if they produce inflammation, then they have the potential to go on to cancer. And many of these metals do*."[251] She did not quantify levels beyond "*very, very low levels*." Again, her testimony that an effect can be claimed without regard to dose is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

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[247] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8; Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Rebecca Smith-Bindman, MD, 11/15/18, p. 5, 16; Expert Report of Mark Krekeler, PhD, 11/16/18, p. 6-7; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.

[248] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 10; Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Rebecca Smith-Bindman, MD, 11/15/18, p. 5, 16; Expert Report of Mark Krekeler, PhD, 11/16/18, p. 6-7; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.

[249] Deposition of Judith Zelikoff, PhD, 1/21/19, 265:6-20.

[250] Deposition of Judith Zelikoff, PhD, 1/21/19, 288:10-15.

[251] Deposition of Judith Zelikoff, PhD, 1/21/19, 282:19-24.

4. Nickel

a. Key opinions

- No association has been found between exposure to nickel and ovarian cancer in humans or animals.
- No conclusions can be drawn regarding the carcinogenicity and/or the carcinogenic potency of nickel from talc (on any organ) without knowledge of the specific bioavailability of nickel from talc.
- The allegation that a trace level of nickel can cause ovarian cancer is not consistent with established scientific knowledge; the US FDA and ICH have both established daily exposure levels that are protective of the public health for all patient populations.
- There are no scientific data supporting the concept that alleged trace levels of nickel in talc products cause ovarian cancer.

b. Overview

Nickel (Ni) is a naturally-occurring element widely dispersed in the environment; it is found in the earth's crust, soil, and emitted from volcanoes. Nickel is combined with other metals to produce alloys or other elements to form nickel compounds.[252] There are a wide range of nickel-containing compounds, including compounds that are insoluble (e.g., nickel sulfide, nickel subsulfide, nickel oxide, nickel carbonyl and nickel carbonate) and soluble (e.g., nickel acetate, nickel chloride, nickel sulfate and nickel nitrate).[253]

Elemental nickel is a hard, lustrous, silvery white material; however, many nickel compounds are green. Neither nickel nor its compounds have a characteristic odor or taste.[254]

c. Exposure sources

Exposure to low levels of nickel can occur through ambient air, water, food and tobacco consumption.[255] Nickel exposure may also result from human activities, such as mining and industrial use.[256] Nickel and/or nickel compounds are used in electroplating, ceramics, pigments, manufacturing of alloy and stainless steel, batteries and coins.[257]

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[252] ATSDR. Toxicological Profile for Nickel. Atlanta, GA. August, 2005; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[253] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019., p. 1130.
[254] ATSDR. Toxicological Profile for Nickel. Atlanta, GA. August, 2005.
[255] ATSDR. Toxicological Profile for Nickel. Atlanta, GA. August, 2005; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[256] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[257] ATSDR. Toxicological Profile for Nickel. Atlanta, GA. August, 2005; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.

For non-smokers, food is the largest source of nickel intake, with the highest concentrations measured in beans, seeds, nuts and grains. [258] Other exposures can include contact with soil, bath or shower water, or metals containing nickel (i.e., jewelry). [259] Occupational exposures result from inhalation, ingestion or skin contact.[260]

d. Current exposure guidelines and standards

Daily human exposure to nickel through food and water intake has been estimated to be 107-109 µg/day for women.[261]

The US FDA and ICH have established permitted daily exposure levels (for nickel as a trace constituent in pharmaceuticals) without risk of adverse health impact via oral, parenteral [injection] and inhalation exposure routes of 220, 22, and 6.0 µg/day, respectively.[262]

The WHO guideline [acceptable] value for nickel in drinking water is 70 µg/L,[263] whereas the allowable level in bottled drinking water in the United States is 100 µg/L total nickel.[264] Assuming consumption of 2 L/day of water, these levels correspond to intake levels of 140 and 200 µg/L, respectively.

e. Animal toxicology studies

Animal studies show nickel is not associated with an increased risk of ovarian cancer. Many carcinogenicity studies have been performed with rodents for a number of different nickel compounds. The discussion below provides results of the NTP inhalation studies as an overview of the types of tumors observed with different compounds.[265]

Inhalation or intratracheal instillation of insoluble nickel compounds (**nickel subsulfide or nickel oxide**) has been associated with dose-related increases in benign and malignant lung

[258] ATSDR. Toxicological Profile for Nickel. Atlanta, GA. August, 2005; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[259] ATSDR. Toxicological Profile for Nickel. Atlanta, GA. August, 2005; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[260] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[261] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[262] US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015; ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014.
[263] WHO. Nickel in drinking-water - Background document for development of WHO guidelines for drinking-water quality. WHO/SDE/WSH/07.08/55. 2007.
[264] FDA. CFR Title 21 Food and Drugs; Part 165 - Beverages. Section 165.110 Bottled water. Code of Federal Regulations. 2016.
[265] Goodman, J.E., Prueitt, R.L., Thakali, S. and Oller, A.R. The nickel ion bioavailability model of the carcinogenic potential of nickel-containing substances in the lung. Critical Reviews in Toxicology. 41(2):142-74, 2011.

tumors, including carcinoma in rats and some mouse studies.[266] None of these studies observed an increased incidence of ovarian neoplasms.

- **Nickel subsulfide** (NTP inhalation study, two years, rats and mice): The two-year inhalation study of rats (0.15 or 1 mg/m^3, 6 hr/day, 5 d/week), observed increased incidence of respiratory tumors and adrenal medulla pheochromocytomas in both sexes of rats. The corresponding two-year study of mice found no evidence of carcinogenic activity in males or females following two-year exposures of 0.6 or 1.2 mg/m^3, 6 hr/day, 5 d/week. In both mice and rats, exposure to nickel subsulfide did not cause an increased incidence of ovarian neoplasms.[267]
- **Nickel oxide** (NTP inhalation study, two years, rats and mice): The two-year inhalation study of rats (0.62, 1.25, or 2.5 mg/m^3, 6 hr/day, 5 d/week), observed some evidence of carcinogenic activity based on an increased incidence of respiratory tumors and adrenal medulla pheochromocytomas in both sexes of rats. The corresponding two-year study of mice found no evidence of carcinogenic activity in males and equivocal evidence of increased respiratory tumors in females following two-year exposures of 1.25, 2.5 or 5 mg/m^3, 6 hr/day, 5 d/week. In both mice and rats, exposure to nickel oxide did not cause an increased incidence of ovarian neoplasms.[268]
- **Nickel sulfate hexahydrate** (NTP inhalation study, two years, rats and mice): The two-year inhalation study of rats (0.12, 0.25, 0.5 mg/m^3, 6 hr/day, 5 d/week), observed no evidence of carcinogenic activity in either sex of rats. Likewise, the corresponding two-year study of mice found no evidence of carcinogenic activity in males or females following two-year exposures of 0.25, 0.5, or 1 mg/m^3, 6 hr/day, 5 d/week. In both mice and rats, exposure to nickel sulfate hexahydrate did not cause an increased incidence of ovarian neoplasms.[269]

Animal carcinogenicity studies of water-insoluble nickel compounds also have found tumors (generally sarcomas) at sites where nickel compounds have been directly injected, including under the skin (subcutaneous), into the muscle (intramuscular), and into the kidney

[266] IARC. Volume 49: Chromium, Nickel and Welding. Geneva: World Health Organization; 1990. p. 687; NTP. Toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 451. July, 1996; NTP. Toxicology and carcinogenesis studies of nickel subsulfide (CAS No. 12035-72-2) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 453. July, 1996; NTP. Nickel Compounds and Metallic Nickel. Fourteenth Report on Carcinogens. Durham, NC. 2016; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.

[267] NTP. Toxicology and carcinogenesis studies of nickel subsulfide (CAS No. 12035-72-2) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 453. July, 1996.

[268] NTP. Toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 451. July, 1996.

[269] NTP. Toxicology and carcinogenesis studies of nickel sulfate hexahydrate (CAS No. 10101-97-0) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 454. July, 1996.

(intrarenal).[270] Doses of injected insoluble nickel ranged from 0.5 mg to >10 mg/animal were associated with development of local tumors, while only some studies of soluble nickel, in doses ranging from 4 to 14 mg/rat, were associated with local tumor development.[271]

Many rodent studies evaluating soluble nickel compounds have not observed increased tumor incidence. No studies have observed ovarian cancer associated with exposure to any nickel compound.[272]

To summarize, no evidence of nickel-induced ovarian cancer has been observed in animal studies using multiple routes of exposure and many different types of nickel compounds.

f. Human cancer studies and conclusions

No human studies have shown a relationship between nickel and ovarian cancer. No regulatory body or scientific organization has concluded that a causal relationship exists between nickel and ovarian cancer.

Although no associations for ovarian cancer were observed, human epidemiologic data for nickel compounds indicate that worker cohorts in nickel industries had increased risk of respiratory cancer. However, data from different cohorts exposed to different nickel compounds suggest that not all nickel compounds may be equally carcinogenic.[273] Types of nickel compounds that have reported increased risk of respiratory cancer in occupational settings include industries processing and refining sulfidic, oxidic, water-soluble and metallic forms of nickel.[274]

Following a comprehensive review, IARC concluded nickel compounds were *carcinogenic to humans* (Group 1). This was based on "*sufficient evidence in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal* [and that these compounds] *cause cancers of the lung, nasal cavity and paranasal sinuses*" and "*other than for lung cancer and nasal sinus cancer, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at other sites.*"[275]

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[270] NTP. Nickel Compounds and Metallic Nickel. Fourteenth Report on Carcinogens. Durham, NC. 2016; IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218; IARC. Volume 49: Chromium, Nickel and Welding. Geneva: World Health Organization; 1990. p. 687.
[271] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218; IARC. Volume 49: Chromium, Nickel and Welding. Geneva: World Health Organization; 1990. p. 687.
[272] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218; IARC. Volume 49: Chromium, Nickel and Welding. Geneva: World Health Organization; 1990. p. 687.
[273] Doll, R. Report of the International Committee on Nickel Carcinogenesis in Man. Scand J Work Environ Health. 16(1 Spec No):1-82, 1990.
[274] Goodman, J.E., Prueitt, R.L., Thakali, S. and Oller, A.R. The nickel ion bioavailability model of the carcinogenic potential of nickel-containing substances in the lung. Critical Reviews in Toxicology. 41(2):142-74, 2011.
[275] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.

The IARC panel's determinations regarding the evidence in animal studies were more complicated. Panel conclusions found, depending on which nickel compound was considered, *sufficient evidence*, *limited evidence*, or *inadequate evidence* for carcinogenicity in animals.[276]

Understanding the mechanism for the carcinogenicity of nickel compounds is complicated by the complexity of nickel compounds. An early theory (hypothesis) was that the nickel ion was the ultimate carcinogen and that "*if it can be released from a nickel-containing substance, then that substance should be considered carcinogenic*."[277] However, animal studies conducted by the NTP (summarized above) disproved that theory, as the nickel compound with the highest solubility (nickel sulfate hexahydrate) showed no evidence of carcinogenic activity in rats or mice; [278] the intermediately soluble compound (nickel subsulfide) showed clear evidence of carcinogenic activities in rats (with inhalation exposures beginning at 0.11 mg nickel/m^3 [0.15 mg/m^3 nickel subsulfide]);[279] and the least soluble compound (nickel oxide) showed some evidence of carcinogenicity in rats (with inhalation exposures beginning at 1.0 mg nickel/m^3 Ni [1.25 mg/m^3 nickel oxide].[280] Since that time, several investigators have proposed that it is the bioavailability of the nickel ion that is responsible, with the specific chemical form of the nickel compound determining whether it can reach the target cell nucleus and cause cancer.[281]

Potency of different nickel compounds was evaluated in a comprehensive, weight-of-evidence analysis that included both *in vitro* and animal carcinogenicity studies. The carcinogenic potency for nickel compounds was consistently related to the bioavailability of nickel ions (from the compound of interest). Because the focus of the studies was inhalation, the bioavailability of nickel ions from different compounds depends upon the compound's respiratory toxicity (e.g., were exposures associated with cytotoxicity), its clearance (e.g., how fast the body cleared it from the lung), intracellular uptake (e.g., how readily cells absorb the compound), and both extracellular and intracellular dissolution (e.g., how readily did the compound dissolve into nickel ions). [282]

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[276] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.
[277] Goodman, J.E., Prueitt, R.L., Thakali, S. and Oller, A.R. The nickel ion bioavailability model of the carcinogenic potential of nickel-containing substances in the lung. Critical Reviews in Toxicology. 41(2):142-74, 2011.
[278] NTP. Toxicology and carcinogenesis studies of nickel sulfate hexahydrate (CAS No. 10101-97-0) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 454. July, 1996.
[279] NTP. Toxicology and carcinogenesis studies of nickel subsulfide (CAS No. 12035-72-2) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 453. July, 1996.
[280] NTP. Toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Toxicology Program technical report series. Report No.: No. 451. July, 1996.
[281] Haber, L.T., Bates, H.K., Allen, B.C., Vincent, M.J. and Oller, A.R. Derivation of an oral toxicity reference value for nickel. Regul Toxicol Pharmacol. 87 Suppl 1:S1-S18, 2017.
[282] Goodman, J.E., Prueitt, R.L., Thakali, S. and Oller, A.R. The nickel ion bioavailability model of the carcinogenic potential of nickel-containing substances in the lung. Critical Reviews in Toxicology. 41(2):142-74, 2011.

To summarize, exposure to nickel has not been associated with ovarian cancer in humans. Current scientific knowledge indicates the carcinogenicity of nickel compounds is not determined by the mere presence of nickel alone, but is determined by the bioavailability of the nickel compound.

g. Alleged levels in talc

There are no scientific data supporting the concept that alleged trace levels of nickel in talc products cause ovarian cancer.

As discussed above, knowledge regarding the bioavailability (the tissue-specific toxicity, clearance, intracellular uptake, and both extracellular and intracellular dissolution of nickel from any nickel-containing compound) is necessary before any hypothesis regarding its carcinogenic potential and/or potency can be put forth regarding tissues (i.e., lungs) known to be associated with nickel-induced carcinogenicity. Claims that alleged trace levels of nickel in talc products can simply release ions and cause cancer are over-simplistic and not supported by published scientific data.

In addition, the allegation that a trace level of nickel can cause ovarian cancer is not consistent with established scientific knowledge; the US FDA and ICH have both established daily exposure levels that are protective of the public health for all patient populations.[283]

Scientific data do not support the concept that alleged levels of nickel in talc products cause ovarian cancer.

h. Critique of nickel evaluation by plaintiffs' experts

Plaintiffs' experts use hazard identification statements (e.g., IARC-assigned human carcinogenicity categorizations) to identify potential hazards (cancer)[284] that they allege may be associated with use of perineal application of talc. However, asserting a hazard identification statement (assigned based on carcinogenicity to non-ovarian tissues), without consideration of the exposure levels necessary for the potential hazard (e.g., nickel in talc) to pose a specific risk to human ovarian cancer, is not consistent with the established methods toxicologists use to conduct risk assessment (see previous report section regarding human health risk assessment, page 9).

Plaintiffs presuppose that nickel in talc products is a hazard, but fail to acknowledge that human exposure to nickel is ubiquitous, and animal studies clearly demonstrate that different nickel compounds exhibit different potential carcinogenicities.[285] Dr. Zelikoff testified that one

[283] US FDA. Guidance for Industry. Q3D Elemental Impurities. September, 2015; ICH. Guideline for elemental impurities Q3D. Step 4 version. December, 2014.
[284] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 10; Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Rebecca Smith-Bindman, MD, 11/15/18, p. 5, 16; Expert Report of Mark Krekeler, PhD, 11/16/18, p. 6-7; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.
[285] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 10; Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 24; Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6; Expert Report of Rebecca Smith-Bindman, MD,

particle of nickel, either inhaled or applied to the perineum, could induce inflammation in the ovaries.[286] Scientifically, the one particle statement is as speculative as it is unverifiable and contradicted by one of her own cited references (Zambelli and Ciruli, 2013), which states "*There is no epidemiological evidence on possible cancer risk from general environmental and dietary nickel exposures*."[287] Her testimony that an effect can be claimed without regard to dose is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

When asked what dose was required (of the whole talcum product) to start the biological process of talc and ovarian cancer, Dr. Zelikoff testified, "*It's unknown, it's not in the literature*."[288] This response implies she has not made any consideration relating to dose of nickel potentially involved in such a process, thereby claiming an effect without regard to dose, which is inconsistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

Dr. Zelikoff failed to incorporate all nickel carcinogenicity studies in her statement that "*in experimental animals, nickel compounds induce tumors at virtually all sites of application (Denkhaus, 2002; IARC, 1987; Zabmelli [sic], 2013).*"[289] While her statement likely represented early research on nickel, it is no longer accurate. For example, the 2012 IARC assessment concludes that the two-year oral study of nickel sulfate hexahydrate in rodents did not result in carcinogenesis and that no carcinogenesis was observed following two years of inhalation exposure in both rats and mice.[290]

5. Fragrances

a. Key opinion

- Scientific data do not support the concept that fragrance ingredients used in Johnson's Baby Powder or Shower to Shower cause ovarian cancer.

b. Overview

The safety of fragrance ingredients used in Johnson's Baby Powder or Shower to Shower is established using a process of Independent Expert Review Panels. This process of independent review panels is generally accepted as definitive.

11/15/18, p. 5, 16; Expert Report of Mark Krekeler, PhD, 11/16/18, p. 6-7; Expert Report of Robert B. Cook, PhD, 11/16/18, p. 3.

[286] Deposition of Judith Zelikoff, PhD, 1/21/19, 315:5-20, 319:23-320:9.

[287] Expert Report of Judith Zelikoff, PhD, 11/16/18; Zambelli, B. and Ciurli, S. Nickel and human health. Ch. 10 In: Interrelations between Essential Metal ions and Human Diseases. Met Ions Life Sci. Vol 13. Sigel, A., Sigel, H., Sigel, R.K.O., editors. New York: Springer; 2013. p. 321-57.

[288] Deposition of Judith Zelikoff, PhD, 1/21/19, 265:6-20.

[289] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 9.

[290] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.

Consumer products contain a multitude of fragrance materials used in personal products (creams, lotions, soaps, etc.) and household products. Each formulated fragrance added to a product may contain up to 300 different ingredients, of which any one or more may be deemed essential by the manufacturer for their product's aesthetic and commercial "edge." Therefore, it is not surprising that "*details of ingredients and formulations are carefully guarded by each proprietary organization*."[291] Due to the proprietary nature of the industry, two international organizations have been and are actively involved in self-regulating fragrance ingredients.

- **Research Institute for Fragrance Materials, Inc. (RIFM):** In 1966, RIFM was established as a science-based, "independent and distinct entity charged with three principal objectives concerning substances used as fragrance ingredients (some with a long history of use):
  - to assure that there are adequate data available to support the safety of these materials under their conditions of use;
  - to review and evaluate standards for testing fragrance ingredients; and
  - to communicate this information to the industry and the scientific community."[292]
- **International Fragrance Association (IFRA):** IFRA was established in 1973 with the goal of "ensuring the highest levels of safety of fragranced products."[293]

In the 40+ years since their inception, these international organizations have worked together to use scientific data to evaluate and/or set usage levels and standards protective of human and environmental health.

Individual fragrance ingredients are evaluated by an RIFM Expert Advisory Panel of scientific experts. Panelist appointment requirements include expertise in dermatology, toxicology, pathology and/or environmental science; independence from the fragrance industry; and a research-based scientific background. RIFM performs safety assessments through first extensively gathering and reviewing all published and unpublished/proprietary data.[294] If necessary, RIFM initiates and organizes any missing safety studies on the fragrance ingredient and performs a safety assessment (also called a risk assessment) to evaluate the data on each fragrance ingredient with the current use levels. RIFM has evaluated more than a thousand fragrance ingredients using a transparent safety assessment process that has evolved over time to reflect the evolution of toxicological principles, methodologies and risk assessment paradigms. All of RIFM's safety assessments have been published in peer-reviewed literature.[295] Hundreds

[291] Bickers, D.R., Calow, P., Greim, H.A., *et al.* The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 37(2):218-73, 2003.
[292] Ford, R.A., Domeyer, B., Easterday, O., Maier, K. and Middleton, J. Criteria for development of a database for safety evaluation of fragrance ingredients. Regul Toxicol Pharmacol. 31(2 Pt 1):166-81, 2000.
[293] International Fragrance Association (IFRA). IFRA and the Industry Self-Regulation Approach. December, 2007.
[294] Bickers, D.R., Calow, P., Greim, H.A., *et al.* The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 37(2):218-73, 2003.
[295] Api, A.M., Belsito, D., Bruze, M., *et al.* Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem Toxicol. 82 Suppl:S1-s19, 2015; Bickers, D.R.,

of monographs on fragrance materials and essential oils were published by RIFM in its early years, followed by a series of safety assessments of groups of fragrance ingredients.[296]

RIFM also maintains an active database of all toxicity information derived during review processes that, in 2003, reportedly included information for 2,665 different fragrance materials.[297]

A collaborative relationship exists between RIFM and IFRA. If a potential concern arises regarding current (maximum) use profiles during RIFM's safety assessment, the RIFM expert panel recommends that IFRA issue a standard to restrict or prohibit use of a material. Therefore, standards are issued on only a subset of RIFM-reviewed ingredients.[298]

IFRA also publishes the *IFRA Transparency List*, which is a register of all fragrance ingredients used in consumer goods by the fragrance industry's customers worldwide. Ingredients on the list include basic substances used for odor and malodor coverage as well as functional ingredients, which provide functionality/durability of a fragrance compound (i.e., added to provide antioxidant or preservative properties, or to serve as a diluent, solvent or pigment).[299] The list, which is compiled every four years using data regarding volume of use surveys submitted by IFRA members, provides anonymous and confidential reporting to the industry's safety assessment program managed by RIFM.[300]

Prioritization of ingredients evaluated by RIFM is systematic and based on volume of use (as a surrogate for potential population exposure), structural similarity to other compounds (whose toxicity has been reviewed) and potential safety alerts triggered by new publications regarding toxicity of ingredients (or structurally similar compounds).[301]

c. Fragrances in Johnson's Baby Powder and Shower to Shower

My review of materials included an evaluation of the fragrance ingredients in Johnson's Baby Powder and Shower to Shower, which included 173 unique fragrance ingredients.[302] The

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Calow, P., Greim, H.A., *et al.* The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 37(2):218-73, 2003.

[296] Surburg, H. and Panten, J. Common Fragrance and Flavor Materials: Preparation, Properties, and Uses. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. 2016.

[297] Bickers, D.R., Calow, P., Greim, H.A., *et al.* The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 37(2):218-73, 2003.

[298] Bickers, D.R., Calow, P., Greim, H.A., *et al.* The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 37(2):218-73, 2003; IFRA. Standards Library. http://www.ifraorg.org/en-us/standards-library#.XEJZxFxKiUk. Accessed: 1/18/2019.

[299] IFRA. IFRA Volume of Use Survey 2016: Transparency List. http://admin-ifra.alligence.com/Upload/Docs/Transparency%20list.pdf. Accessed: 1/18/2019. ; IFRA. Ingredients and Transparency. http://admin-ifra.alligence.com/Upload/Docs/Transparency%20list.pdf. Accessed: 1/18/2019.

[300] IFRA. Ingredients and Transparency. http://admin-ifra.alligence.com/Upload/Docs/Transparency%20list.pdf. Accessed: 1/18/2019.

[301] Bickers, D.R., Calow, P., Greim, H.A., *et al.* The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 37(2):218-73, 2003.

[302] Exhibit 1; Exhibit 2; Exhibit 3 [Attorneys' Eyes Only].

combination of all products was less than or equal to 0.22% in Johnson's Baby Powder[303] and a maximum of 1% in Shower to Shower.[304] Many of these fragrance ingredients are listed with multiple CAS (Chemical Abstracts Service) numbers. Despite the multiple CAS number designations, the fragrances are considered a single ingredient. All of the Johnson's Baby Powder and Shower to Shower fragrance ingredients (with one possible exception)[305] are listed on the *IFRA Transparency List*,[306] indicating their current known use as fragrance ingredients in consumer products.

Of the 173 fragrance ingredients, at least 157 have been evaluated by RIFM (i.e., have published safety assessments). For the majority (119/157) of the RIFM-evaluated fragrance ingredients, IFRA chose not to issue standards, indicative that its review concluded that use of these fragrance ingredients do not pose an increased risk of adverse health, including ovarian cancer. IFRA standards are published in the *IFRA Standards Booklet, 48th Amendment* and associated Annexes. IFRA restriction standards were available for 35 of the fragrance ingredients.[307] The documents I reviewed demonstrated that all the fragrance ingredients in this category were within the use limits and do not pose an increased risk of adverse health effects, including ovarian cancer.

No data indicated that ovarian cancer was associated with any of the 16 fragrance ingredients for which there was no clear RIFM review. Reviews were performed January 14-18, 2019, using PubMed and Google search engines. Six (6) were recognized as GRAS (generally recognized as safe) for food. Information regarding carcinogenicity (observed in any organ) for the ingredients is presented in Table 10.

Scientific data do not support the concept that use of any of these fragrance ingredients in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

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[303] JNJ 000062074; JNJ 000135310; JNJTALC000126896; J&J-0037140; IMERYS 209327; J&J-0037168; IMERYS 209355; J&J-0037168; IMERYS 209355; J&J-0037178; IMERYS 209365; J&J-0037189; IMERYS 209376; JNJ000350173; JNJ000350192; JNJ000350194; JNJ 000350198; JNJ 000350210.

[304] JNJ 000455029; JNJ 000455031; JNJ 000455099; JNJ 000455106; JNJ000455407; JNJ 000455120; JNJ 000455127; JNJ 000455301; JNJ 000455333; JNJ 000455363; JNJ 000455167; JNJTALC000126897-905; JNJTALC000126926; JNJTALC000127100; JNJTALC000127133; JNJTALC000127151; JNJTALC000127169; JNJTALC000127104; JNJTALC000127107; JNJTALC000127122; JNJTALC000127140; JNJTALC000127158; JNJTALC000127176; JNJTALC000127119; JNJTALC000127137; JNJTALC000127155; JNJTALC000127173.

[305] Copper Chlorophyll (CAS #24111-17-9) was not found on *IFRA Transparency List*, although list included entries for similar compounds (1) copper, [dihydrogen 21-carboxy-14-ethyl-4,8,13,18-tetramethyl-20-oxo-9-vinyl-3-phorbinepropionato(2-)]-, 21-methyl phytyl ester, (E)- (CAS#15739-09-0); and (2) copper chlorophyllin, sodium complex (CAS# 11006-34-1).

[306] IFRA. IFRA Volume of Use Survey 2016: Transparency List. http://admin-ifra.alligence.com/Upload/Docs/Transparency%20list.pdf. Accessed: 1/18/2019.

[307] IFRA published specification standards for three of the evaluated fragrances.

Table 10: Review of *IFRA Transparency List* fragrance chemicals without a clear RIFM review history used in Johnson's Baby Powder and Shower to Shower

Fragrance	CAS #	Literature search for carcinogenicity
1,1'-Oxybis-2-propanol	110-98-5	No evidence for carcinogenicity in any organ; NTP: When assessed as a mixture of isomers: "*no evidence of carcinogenic activity*" in both sexes of rats and mice[308]
3-(5,5,6-Trimethylbicyclo[2.2.1]hept-2-yl)cyclohexanol	3407-42-9	No evidence for carcinogenicity in any organ
Boswellia Carterii Oil (a.k.a. Frankencense)	8050-07-5	No evidence for carcinogenicity in any organ
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol	65113-99-7	No evidence for carcinogenicity in any organ
1,2-Dimethoxybenzene	91-16-7	No evidence for carcinogenicity in any organ
Benzoic acid, 2,4-dihydroxy-3,6-dimethyl-, methyl ester (veramoss)	4707-47-5	No evidence for carcinogenicity in any organ
Ethenylbenzene (styrene)	100-42-5	[see discussion later in this report]
Butanoic acid, pentyl ester (n-Amyl butyrate)	540-18-1	No evidence for carcinogenicity in any organ
Copper Chlorophyll	24111-17-9	No evidence for carcinogenicity in any organ
Tartaric Acid	133-37-9, 147-71-7, 87-69-4	No evidence for carcinogenicity in any organ
Aloe Barbadensis Leaf Extract (Aloe vera)	85507-69-3, 94349-62-9	IARC: whole leaf extract of *Aloe vera (barbadensis)* is possibly carcinogenic to humans (Group 2B) based on inadequate (no) human data and increased carcinoma incidence in rat large intestine with oral exposure[309] NTP: "clear evidence of carcinogenic activity" in rats and "no evidence of carcinogenic activity" in mice[310]
Propylene Glycol	57-55-6	No evidence for carcinogenicity in any organ
Tromethamine	77-86-1	No evidence for carcinogenicity in any organ
Indisan (Sandela) reaction product	70955-71-4	No evidence for carcinogenicity in any organ

[308] NTP. Toxicology and carcinogenesis studies of dipropylene glycol (CAS 25265-71-8) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park, NC. NTP Technical Report. Report No.: NTP TR 511. June, 2004.
[309] IARC. Aloe vera. In: Vol 108 – Some Drugs and Herbal Products. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon, France: World Health Organization International Agency for Research on Cancer; 2016. p. 37-71.
[310] NTP. Toxicology and Carcinogenesis Studies of a Nondecolorized Whole Leaf Extract of Aloe Barbadensis Miller (Aloe Vera) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). Research Triangle Park, NC. Report No.: NTP TR 577. August, 2013.

Fragrance	CAS #	Literature search for carcinogenicity
t-Butyl hydroquinone	1948-33-0	No evidence for carcinogenicity in any organ; NTP: When assessed as a mixture of isomers: "*no evidence of carcinogenic activity*" in both sexes of rats and mice[311]
3-(Hydroxymethyl)-2-nonanone	67801-33-6	No evidence for carcinogenicity in any organ

d. Critique of plaintiffs' experts' fragrance ingredient evaluation

Dr. Crowley testified that he was not asked to consider dose response in this case and he was unable to do so based on the information given to him.[312] However, maximum concentrations of fragrance ingredients in Johnson's Baby Powder and Shower to Shower were provided in the documents listed in his report. Specifically, the formulation documentation shows Johnson's Baby Powder contained a maximum of 0.22% fragrance ingredients.[313] Similar documentation for Shower to Shower shows its various formulations contained a maximum of 1% fragrance.[314] Maximum concentrations of fragrance ingredients in products could have been calculated using the maximum overall specification for fragrance (%) with the maximum specification for each ingredient on the protected fragrance ingredient lists (conservatively assuming percentage units).[315]

i) Dr. Crowley's method for relying solely on hazards without consideration of dose when forming his opinion is scientifically flawed and not a generally accepted scientific methodology

Dr. Crowley testified that he did not undertake a risk assessment and was not asked to identify a hazard.[316] However, his report lists various hazards (e.g., irritation, sensitization, allergenicity, reproductive and developmental effects and potential carcinogenicity) associated with fragrance ingredients to inform his opinion regarding their contributions to the inflammatory properties, toxicity, and potential carcinogenicity of the products.[317] As explained above, using hazard alone to establish a risk of adverse effects (such as irritation, sensitization, allergenicity, reproductive and developmental effects and potential carcinogenicity), without

[311] NTP. Toxicology and Carcinogenesis Studies of t-Butylhydroquinone (CAS 1948-33-0) in F344/N Rats and B6C3F1 Mice (Feed Studies). Report No.: No. 459. May, 1997.
[312] Depostiton of Michael Crowley, PhD, 1/4/19, 123:16-20, 123:22-124:1, 126:2-12.
[313] JNJ 000062074; JNJ 000135310; JNJTALC000126896; J&J-0037140; IMERYS 209327; J&J-0037168; IMERYS 209355; J&J-0037168; IMERYS 209355; J&J-0037178; IMERYS 209365; J&J-0037189; IMERYS 209376; JNJ000350173; JNJ000350192; JNJ000350194; JNJ 000350198; JNJ 000350210.
[314] JNJ 000455029; JNJ 000455031; JNJ 000455099; JNJ 000455106; JNJ000455407; JNJ 000455120; JNJ 000455127; JNJ 000455301; JNJ 000455333; JNJ 000455363; JNJ 000455167; JNJTALC000126897-905; JNJTALC000126926; JNJTALC000127100; JNJTALC000127133; JNJTALC000127151; JNJTALC000127169; JNJTALC000127104; JNJTALC000127107; JNJTALC000127122; JNJTALC000127140; JNJTALC000127158; JNJTALC000127176; JNJTALC000127119; JNJTALC000127137; JNJTALC000127155; JNJTALC000127173.
[315] Attorneys Eyes Only Documents, Exhibit 1, Exhibit 2, Exhibit 3.
[316] Depostiton of Michael Crowley, PhD, 1/4/19, 123:16-20, 123:22-124:1.
[317] Expert Report of Michael M. Crowley, PhD, 11/12/18.

consideration of potential levels of exposure (dose), is not scientifically valid. Valid human health risk assessments identify potential hazards, then consider what levels of exposure need to be reached for those hazards to pose a risk to human health. Similarly, levels of exposure are a necessary component to draw conclusions regarding initiation of biological effects associated with the hazards identified by Dr. Crowley. Use of hazard identification statements alone, without knowledge, analysis, and assessment of exposure levels associated with adverse effects and those estimated for the population under evaluation, is not consistent with the generally accepted methods used by toxicologists to assess potential risk to human health. Dr. Crowley acknowledged that he "*is not aware of an epidemiology study substantiating the causation of ovarian cancer from so-called fragrance chemicals*."[318]

In his expert report, Dr. Crowley specifically "*identified several chemicals in the fragrance mixture used by J&J in the talcum products with studies, in vitro and in vivo, published in peer reviewed journals demonstrating carcinogenicity, developmental or reproductive toxicity, genotoxicity, and or mutagenicity*."[319]

Below, I provide additional toxicological information regarding the fragrance ingredients discussed by Dr. Crowley and explain why there is a lack of scientific data to support any concern that these ingredients can cause ovarian cancer.

Coumarin (CAS 91-64-5)

Scientific data do not support Dr. Crowley's concern that use of coumarin as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer. Use of coumarin as a fragrance ingredient was of concern to Dr. Crowley because it was an IARC Group 3 carcinogen.[320] However, as explained in my earlier explanation of IARC's methodology and conclusions (see page 14), an IARC Group 3 carcinogenicity classification indicates a lack of scientific data for any conclusion regarding carcinogenicity (i.e., coumarin was *not classifiable* as to its carcinogenicity to humans). My independent evaluation found no scientific data indicating coumarin is a cause of ovarian cancer. Specifically:

- Coumarin is used as a fragrance in both the perfume and cosmetic industries and is used in a wide variety of personal products, including hand soaps, detergents, lotions and perfumes at concentrations usually from 0.01 to 0.8%. It is naturally present at relatively high levels in essential oils such as cinnamon leaf oil, cinnamon bark oil, peppermint oil and lavender oil.[321]
- My review of numerous studies, as part of a comprehensive, peer-reviewed human risk assessment, concluded that the scientific dataset indicates:
  - Coumarin is not a genotoxic agent;

[318] Deposition of Michael Crowley, PhD, 1/4/19, 196:7-19.
[319] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 12.
[320] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 13.
[321] IARC. Coumarin. In: Volume 77 - Some Industrial Chemicals. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France 2000. p. 193-225.

- Coumarin did not induce any ovarian cancer in animal studies (when observed, carcinogenic effects were limited to the liver and lung); and
- Liver and lung tumors were only observed in rats and mice at relatively high doses (i.e., doses high enough to elicit a more generalized coumarin-induced toxicity reaction). Because the concentration needed to reach a level for which gross changes were observed before carcinogenicity occurred, the dose-response for coumarin was concluded to be non-linear (i.e., have a threshold below which no carcinogenic effects occur).[322]

Scientific data do not support Dr. Crowley's concern that use of coumarin as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

Benzophenone (CAS 19-61-9)

Scientific data do not support Dr. Crowley's concern that use of benzophenone as a fragrance ingredient in Johnson's Baby Powder or Shower to Shower causes ovarian cancer. Use of benzophenone as an ingredient concerned Dr. Crowley because "*Benzophenone has been classified by IARC as a Group 2B possible human carcinogen*."[323] My scientific assessment evaluation found no scientific data indicating benzophenone is a cause of ovarian cancer. Specifically:

- Benzophenone is used as a fragrance enhancer and flavor ingredient, and is found naturally in food, including wine grapes, black tea and mountain papaya.[324]
- Benzophenone has not been associated with cancer in humans (i.e., no data are available to evaluate).[325]
- Benzophenone (up to 65 mg/kg in rats; 150 mg/kg in mice) did not induce any ovarian cancer in NTP rodent studies (when observed, carcinogenic effects were limited to the liver and kidney in rats and mice).[326]
- In rats whose ovaries had been surgically removed, benzophenone exhibited some estrogenic activity following repeated doses (three daily doses) of 400 mg/kg. The effect was not observed with doses of 100 mg/kg.[327] Results were of uncertain significance given the small number of animals tested and the dose required for the effect (400 but not

[322] Lake, B.G. Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment. Food Chem Toxicol. 37(4):423-53, 1999.
[323] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 13, 48.
[324] IARC. Volume 101: Some chemicals present in industrial and consumer products, food and drinking water. Lyon. Report No.: Volume 101. 2013.
[325] IARC. Volume 101: Some chemicals present in industrial and consumer products, food and drinking water. Lyon. Report No.: Volume 101. 2013.
[326] Rhodes, M.C., Bucher, J.R., Peckham, J.C., *et al.* Carcinogenesis studies of benzophenone in rats and mice. Food Chem Toxicol. 45(5):843-51, 2007.
[327] EFSA CEF Panel. Scientific Opinion on Toxicological evaluation of benzophenone. Adopted 14 May 2009. EFSA Journal. 1104:1-30, 2009.

100 mg/kg) because a daily dose of 65 mg/kg was associated with decreased body weights in the chronic study of female rats.[328]

- EFSA's review of available carcinogenicity studies concluded benzophenone caused liver adenomas at a dose of 40 mg/kg/day, but this effect was less sensitive than the kidney effects. EFSA concluded benzophenone was associated with kidney adenoma in rats and used this non-cancer endpoint as the adverse effect from which to calculate their tolerable daily intake. EFSA's derived tolerable daily intake (TDI) was 0.03 mg/kg.[329]

Scientific data do not support Dr. Crowley's concern that use of benzophenone as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

In his expert report, Dr. Crowley claims that "*Benzophenone was recently removed from use in foods by FDA due to histiocytic sarcoma observed in ovaries and uterus, higher incidences of kidney tumors and leukemia in animal studies, and* in vivo *estrogenic activity*" *[emphasis added]*."[330] Dr. Crowley misrepresented both study outcome and the FDA's ruling in his statement regarding benzophenone. As explained on page 92, his statement about the FDA's removal of benzophenone from use in foods misrepresented both the science (by intentionally omitting the pervasiveness of the cancer of hematopoietic origin) and the details of the FDA's ruling on benzophenone (which was removed as a matter of law under the Delaney Clause, despite FDA's scientific assessment and conclusion that its use as a food additive did not pose a risk to public health).

In short, Dr. Crowley's assertion that the FDA removed benzophenone from use as a food flavoring "*due to histiocytic sarcoma observed in ovaries and uterus [emphasis added]*" is simply untrue.

p-Cresol (CAS: 106-44-5)

This ingredient was of a concern to Dr. Crowley because the U.S. Environmental Protection Agency considers p-cresol, also known as 4-methylphenol, to be "possibly carcinogenic."[331] My independent evaluation found no scientific data indicating that p-cresol is a cause of ovarian cancer.

The US EPA ranked p-cresol as a "Group C" (possible) carcinogen, which corresponds to limited animal data and little or no human data that support a carcinogenic mode of action. US EPA's conclusion was last reviewed in 1990.[332] In a more recent review (2008), ATSDR concluded: "*According to EPA's updated criteria for assessing carcinogenicity of chemicals*

[328] NTP. Toxicology and carcinogenicity studies of benzophenone (CAS 119-61-9) in F344/N rats and B6C3F1 mice (feed studies). Durham, NC. Report No.: No. 533. 2006.
[329] EFSA CEF Panel. Scientific Opinion on Toxicological evaluation of benzophenone. Adopted 14 May 2009. EFSA Journal. 1104:1-30, 2009.
[330] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 48, 65.
[331] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 13, 21, 64.
[332] EPA. 4-Methylphenol, CASRN 106-44-5. 2002; EPA. Cresol/Cresolyic Acid (o-Cresol, m-Cresol, p-Cresol) Hazard Summary. 2000.

(EPA 2005c), cresols fall in the category of chemicals for which there is 'inadequate information to assess carcinogenic potential.'"[333]

No ovarian tumors were observed in NTP's chronic, two-year carcinogenesis studies of a mixture of 60:40 m-/p-cresol of rats and mice. No cancer was noted in rats; mice in the highest exposure group exhibited increased incidence of squamous cell papilloma in the forestomach. Cresols were negative for genotoxicity in bacterial mutation assays.[334]

Scientific data do not support Dr. Crowley's concern that use of p-cresol as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

Eugenol (CAS 97-53-0)

This ingredient was of concern to Dr. Crowley because it was an IARC Group 3 carcinogen.[335] However, as explained earlier in my report (see section E.5.b, page 14), IARC Group 3 classification indicates a lack of scientific data for any conclusion regarding carcinogenicity (i.e., eugenol was *not classifiable* as to its carcinogenicity to humans). My independent evaluation found no scientific data indicating eugenol is a cause of ovarian cancer. Specifically:

- Eugenol, a natural component of many foods, including apples, cloves, bananas and fish, is used as a fragrance and flavoring agent in both the perfume and cosmetic industries and as a dental analgesic.[336] It is naturally present in many plants, and can occur at relatively high levels in many natural components, including basil and cloves; and dietary exposures occur in a variety of sources, from baked goods to meat products.[337]
- My review of numerous studies, as part of a comprehensive, peer-reviewed human risk assessment, concluded that the scientific dataset indicates:
  - Eugenol is not a genotoxic agent;
  - Eugenol has not been associated with cancer in humans (i.e., no data are available to evaluate);[338]
  - Eugenol did not induce any ovarian cancer in animal studies (when observed, carcinogenic effects were limited to the liver); and
  - Eugenol did not induce any exposure-related tumors in the chronic rat study, and the only tumors potentially related to eugenol in the mouse study were observed

[333] ATSDR. Toxicological Profile for Cresols. Atlanta, GA: U.S. Department of Health and Human Services Public Health Service; 2008.
[334] NTP. Toxicology and carcinogenicity studies of cresols (CAS 1319-77-3) in F344/N rats and B6C3F1 mice (feed studies). Durham, NC. Report No.: No. 550. 2008.
[335] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 12.
[336] Api, A.M., Belsito, D., Bhatia, S., *et al.* RIFM fragrance ingredient safety assessment, Eugenol, CAS Registry Number 97-53-0. Food Chem Toxicol. 97s:S25-S37, 2016; IARC. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Allyl Compounds, Aldehydes, Epoxides and Peroxides. Volulme 36. 1985.
[337] IARC. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Allyl Compounds, Aldehydes, Epoxides and Peroxides. Volulme 36. 1985.
[338] IARC. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. 1987.

> in the liver. Results were deemed equivocal because no dose-response was observed in males and there were marginal combined increases in females. The lowest dose in the mouse study was 300 mg/kg/day.[339]

Scientific data do not support Dr. Crowley's concern that use of eugenol as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

d-Limonene (CAS: 138-86-3)

This ingredient was of concern to Dr. Crowley because it was an IARC Group 3 carcinogen.[340] However, as explained earlier in my report (see section E.5.b, page 14), IARC Group 3 classification indicates a lack of scientific data for any conclusion regarding carcinogenicity (i.e., d-limonene was *not classifiable* as to its carcinogenicity to humans). My independent evaluation found no scientific data indicating d-limonene is a cause of ovarian cancer.

The IARC evaluation indicated d-limonene is naturally found in citrus and a variety of other plants that humans are exposed to as part of their diet. Conclusions of the IARC Working Group included: (1) inadequate evidence of carcinogenicity in humans based on the complete lack of data for any association between human exposure to d-limonene and any type of cancer; and (2) sufficient evidence of carcinogenicity in experimental animals based on kidney tumors observed in male rats. However, IARC's overall evaluation as Group 3 (not classifiable), was made following IARC's conclusion that the mechanism for male rat kidney carcinogenicity was not relevant to humans.[341]

Scientific data do not support Dr. Crowley's concern that use of d-limonene as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

Musk ketone (CAS 81-14-1)

Dr. Crowley stated "*Musk ketone is suspected of being a carcinogen, and has been classified as a Category 3 carcinogen by the Scientific Committee on Health and Environmental Risks (SCHER) in Europe*."[342] My independent evaluation found no scientific data indicating musk ketone is a cause of ovarian cancer.

The basis of the SCHER panel classification for musk ketone as a Category 3 carcinogen (i.e., a substance with limited evidence of a carcinogenic effect)[343] was a process called "read across." Read across assigns toxicity data from one compound (for which data are available) to

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[339] Api, A.M., Belsito, D., Bhatia, S., *et al.* RIFM fragrance ingredient safety assessment, Eugenol, CAS Registry Number 97-53-0. Food Chem Toxicol. 97s:S25-S37, 2016.
[340] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 13.
[341] IARC. d-Limonene. In: Vol 73 - Some Chemicals that Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon, France 1999. p. 307-27.
[342] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 13, 48, 51, 65.
[343] European Commission. Chemicals at work - a new labelling system: Guidance to help employers and workers to manage the transition to the new classification, labelling and packaging system. Luxembourg: Publications Office of the European Union. 2013.

another compound (for which data are not available) based on chemical and/or biological similarities between the compounds.[344] In this case, the toxicity for musk ketone was assigned based on data available for a similar chemical (i.e., musk xylene). Musk xylene's Category 3 classification was "*a borderline case since [the observed] increase in liver tumours in the highly sensitive B6C3F1 mouse [was] considered of little relevance for human hazard assessment*."[345] In addition, musk ketone is an established fragrance and the European Union Risk Assessment, which acknowledged the Category 3 classification and found no need for risk reduction measures to reduce exposures below those currently associated with fragrance use; exposures were assumed to occur through daily use of consumer products such as body lotion, face cream and perfume.[346]

Scientific data do not support the concept that use of musk ketone as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

Myroxylon Pereirae (Balsam Peru) Oil (CAS: 8007-00-9)

Dr. Crowley is incorrect in his assertion that Myroxylon Pereirae (Balsam Peru) Oil "*is prohibited by the International Fragrance Association (IFRA) for use as a fragrance ingredient*."[347] In deposition testimony, Dr. Crowley was initially unaware that Balsam Peru extract/distillates (restricted) and Balsam Peru crude (prohibited) shared a CAS Number but were treated differently by IFRA Standards.[348] After clarification of the issue, he offered to update his report.[349]

- IFRA allows use of "Myroxylon pereirae (Balsam Peru) oil" as a standard. Its IFRA standard specifies the use of "Peru balsam crude" is prohibited in a separate standard.[350]

Dr. Crowley correctly specified "Myroxylon pereirae (Balsam Peru) oil" was listed on the FDA Inactive Ingredient Database (IID). Specifically, the database indicates that the FDA has approved the use of Balsam Peru (CAS 8007-00-9) as an inactive ingredient at a level of 100 mg/dose (as a rectal suppository),[351] which corresponds to a daily dose of 1.7 mg/kg (for a 60-kg human).

This review indicates this ingredient is acceptable for use as a fragrance and anticipated levels are well below those acceptable for use in US pharmaceutical products. Scientific data do

[344] OECD. Grouping of chemicals: Chemical categories and read-across. http://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm. Accessed: February 19, 2019.
[345] European Commision Directorate-General Health and Consumer Protection. Scientific Committee on Health and Environmental Risks (SCHER) Opinion on Classification of Musk ketone. 2006., p. 3.
[346]European Chemicals Bureau. European Union Risk Assessment Report 4'-tert-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone (musk ketone). The Netherlands. 2005., p.VII, 48.
[347] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 12.
[348] Deposition of Michael Crowley, PhD, 1/4/19, 169:22-173:11.
[349] Deposition of Michael Crowley, PhD, 1/4/19, 173:16-174:3.
[350] IFRA. IFRA Standard - Peru balsam extracts and distillates. 2009.
[351] US FDA. Inactive Ingredient Search for Approved Drug Products. Balsam Peru. https://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm?event=BasicSearch.page. Accessed: January 15, 2019.

not support the concept that use of Balsam Peru as a fragrance ingredient in talc causes ovarian cancer.

Styrene

Dr. Crowley indicated styrene was of particular concern because it "*has been implicated as reproductive toxicant, neurotoxicant, and has been demonstrated to be a carcinogen in vivo and in vitro. Styrene is listed as such by several governmental and regulatory bodies (RTECS, Prop 65 among others). The National Toxicology Program considers styrene to be 'reasonably anticipated to be a human carcinogen' (The National Toxicology Program (NTP), 2016).*"[352] My independent evaluation found no scientific data indicating styrene is a cause of ovarian cancer.

Data the NTP considered to conclude that styrene was "reasonably anticipated to be a human carcinogen" were based on data from human and animal studies.

- Workers exposed to styrene have shown increased mortality from or increased cancer of the lymphohematopoietic system (e.g., leukemia, lymphoma or a combination) and some increased cancer of the esophagus and pancreatic cancer. However, associations were inconsistent across studies due to different study designs, potential misdiagnoses and co-exposures to other solvents. NTP concluded there was limited evidence for carcinogenicity of styrene in humans.[353]

- Styrene was reasonably anticipated to be a carcinogen by the NTP based on lung tumors in mice following inhalation and oral exposure studies. Observations of cancer in rat studies were inconsistent; mammary tumors were associated with both increased and decreased incidence in treated rats in different studies that had evaluated the same strain of rat. No lung cancer was observed in treated rats.[354]

Scientific data do not support the concept that use of styrene as a fragrance ingredient in Johnson's Baby Powder and Shower to Shower causes ovarian cancer.

ii) Dr. Crowley's suggestion that the inability to test on humans (because it is unethical) is the reason we lack knowledge about the effect of fragrance chemicals on human ovaries contradicts the generally accepted method of animal toxicity testing used by toxicologists

Dr. Crowley repeatedly testified that the lack of knowledge about the effect of fragrance chemicals on human ovaries is a result of being unable to conduct tests on human ovaries.[355] This repeated statement suggests that Dr. Crowley has a fundamental lack of understanding of the basics of toxicology, the use of animal studies, and the relevance of epidemiology data in the science of toxicology in determining the potential risk to human health from any agent. Toxicologists routinely perform hazard identification using animal study data. Human data can

[352] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 13.
[353] NTP. Styrene. Fourteenth Report on Carcinogens, Ed. Durham, NC. 2016.
[354] NTP. Styrene. Fourteenth Report on Carcinogens, Ed. Durham, NC. 2016.
[355] Deposition of Michael Crowley, PhD, 1/4/19, 221:20-222:7; 282:5-12;283:12-20; 285:2-9; 320:14-321:7; 364:7-15.

be nonexistent and limited to case reports of poisonings, and epidemiology studies that suffer from uncertainty regarding doses and confounding by multiple chemical exposures and biases.[356] NTP animal carcinogenicity studies have identified several agents exhibiting positive or clear evidence of carcinogenicity in the ovaries of rodent models.[357] These chemicals include 5-nitroacenaphthene,[358] 1,3-butadiene,[359] benzene,[360] 4-vinylcyclohexene,[361] nitrofurazone,[362] nitrofurantoin,[363] n-methylolacrylamide,[364] 4-vinyl-1-cyclohexene diepoxide,[365] urethane,[366] and acrylamide.[367]

6. Additional concerns regarding plaintiffs' experts' opinions

a. Fundamental toxicology-based concerns

A review of the plaintiffs' experts' reports clearly shows that plaintiffs' experts did not adhere to fundamental principles of toxicology or use generally accepted methodology when developing their expert opinions. As explained above in the risk assessment section (beginning on page 9), hazard identification is the first of four steps conducted by a toxicologist during a human health risk assessment. As detailed below, plaintiffs' experts' use of hazard identification

[356] Ballantyne, B., Marrs, T.C. and Syversen, T. General and Applied Toxicology. 3rd ed.: John Wiley and Sons, Ltd. 2009., p. 2656.
[357] NTP. Organ Sites with Neoplasia. https://manticore.niehs.nih.gov/organsites/. Accessed: 2/1/2019.
[358] NCI. Bioassay of 5-nitroacenaphthene for possible carcinogenicity (CAS No. 602-87-9). Bethesda, MD. National Institutes of Medicine, Report No.: NCI-CG-TR-118. 1978.
[359] National Toxicology Program and National Institutes of Health. NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). Research Triangle Park, NC. NTP 83-071, NIH Publ No 84-2544. Report No.: 288. August, 1984; NTP. Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 434. May, 1993.
[360] NTP. Toxicology and carcinogenesis studies of benzene (CAS No. 71-43-2) in F344/N rats and B6C3F1 mice (gavage studies). Technical report series no. 289. Research Triangle Park, NC. NIH, National Toxicology Program technical report series. April, 1986.
[361] NTP. Toxicology and carcinogenesis studies of 4-vinylcyclohexene (CAS No. 100-40-3) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle, NC. National Institutes of Health, Report No.: NTP TR 303. August, 1986.
[362] NTP. Toxicology and carcinogenesis studies of nitrofurazone (CAS 59-87-0) in male F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 337. June, 1988.
[363] NTP. Toxicology and carcinogenesis studies of nitrofurantoin (CAS No. 67-20-9) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 341. September, 1989.
[364] NTP. Toxicology and carcinogenesis studies of n-methylolacrylamide (CAS No. 924-42-5) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 352. September, 1989.
[365] NTP. Toxicology and carcinogenesis studies of 4-vinyl-l-cyclohexene diepoxide (CAS No. 106-87-6) in F344/N rats and B6C3F1 mice (dermal studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 362. November, 1989.
[366] NTP. Toxicology and carcinogenesis studies of urethane, ethanol, and urethane/ethanol (urethane, CAS No. 51-79-6; ethanol, CAS No. 64-17-5) in B6C3F1 mice (drinking water studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 510. August, 2004.
[367] NTP. Toxicology and carcinogenesis studies of acrylamide (CAS No. 79-06-1) in F344/N rats and B6C3F1 mice (feed and drinking water studies). Research Triangle Park, NC. National Institutes of Health, Report No.: NTP TR 575. July, 2012.

statements alone, without knowledge, analysis and assessment of exposure levels associated with adverse effects and those estimated for the population under evaluation, is not consistent with the generally accepted methods used by toxicologists to assess potential risk to human health.

i) Dr. Plunkett confuses elements of a risk assessment and her assertion that assessment of causation is not part of human health risk assessment is not consistent with generally accepted methods used by toxicologists.

Dr. Plunkett's expert report indicated that her opinions were based on human health risk assessment, which, as she specified, is conducted in "four basic steps: hazard identification, dose-response assessment, exposure analysis, and characterization of risks (NRC, 1983)."[368] However, she testified that she did not perform a general causation analysis in reaching her "opinion that Johnson's baby powder increases the risk of cancer - - ovarian cancer."[369] She attempted to clarify that although the types of information considered for a full causation analysis and a human health risk assessment may overlap, "the outcome or the statements or the - - the way you go about assessing the information is a bit different."[370] She also stated that her "goal was not to analyze the data under the Hill considerations" as part of her human health risk assessment.[371]

Dr. Plunkett's exclusion of causation analysis (and the Bradford Hill criteria for causation) as part of a risk assessment contradicts generally-recognized scientific approaches. For example:

- The *NRC Risk Assessment for the Federal Government – Managing the Process* (1983; the citation used by Dr. Plunkett above) defines hazard identification as "the determination of whether a particular chemical is or is not **causally linked** to particular health effects [emphasis added]."[372]
- The US EPA Guidelines for Carcinogen Risk Assessment specify that the hazard identification step of risk assessment must include a critical assessment of evidence of causality and that "it is appropriate to draw from those aspects initially presented in Hill's classic monograph (Hill, 1965) and widely used by the scientific community in conducting such evidence-based reviews."[373]

As defined above (see page 9), the first step in a risk assessment is hazard identification, which uses the Bradford Hill criteria for causation to identify adverse health effect(s) caused by an agent that subsequent steps of the risk assessment will strive to mitigate. Dr. Plunkett's

[368] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 7.
[369] Deposition of Laura Plunkett, PhD, DABT, 12/19/18, 34:7-21.
[370] Deposition of Laura Plunkett, PhD, DABT, 12/19/18, 33:22-35:21.
[371] Deposition of Laura Plunkett, PhD, DABT, 12/19/18, 36:23-24.
[372] National Research Council. Risk Assessment in the Federal Government – Managing the Process. Washington DC: National Academy Press. 1983.
[373] US EPA. Guidelines for Carcinogen Risk Assessment. Washington, DC. Report No.: EPA/630/P-03/001F. March, 2005.

assertion that assessment of causation is not part of human health risk assessment is inconsistent with generally accepted methods used by toxicologists.

ii) Because Dr. Plunkett did not consider the nature and magnitude of doses associated with human risk, her analysis is not consistent with generally accepted scientific methodology.

Dr. Plunkett stated that she performed a human health risk assessment to generate her opinions.[374] However, her conclusions lack any estimate of risk (the probability that ovarian cancer will occur for any given level of exposure). Dr. Plunkett testified that as part of her weight-of-evidence analysis of results from human studies, she was quantifying whether or not she believed the risk for ovarian cancer was increased above a background risk; however, she did not give the increased risk a number, such as a cancer potency factor.[375] She testified that she did not calculate a risk factor, such as a cancer potency factor, because "I don't have the data, the studies … to allow me to do that."[376] But without an analysis of the nature and magnitude of doses associated with human risk, Dr. Plunkett's evaluation was merely an extensive hazard assessment that provided no information on risk. Reliance on hazard identification alone, without consideration of the levels of exposure necessary for the hazard to pose a cancer risk, is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

iii) Because Dr. Carson did not consider the nature and magnitude of doses associated with human risk, his analysis is not consistent with generally accepted scientific methodology.

Dr. Carson's analysis is a shallow account of asserted arguments made in favor of a potential association/causation between perineal talc use and ovarian cancer. Literature citations are limited to only publications supportive of his opinion and lack any information regarding the extent of analysis required to inform his opinions. For example, his review of chromium, cobalt, and nickel included the statement that they "*are recognized as cancer causing*" and that "*Johnson & Johnson's talcum powder products contain nickel (group 1 human carcinogen), chromium (Group 1 human carcinogen), and cobalt (Group 2B-possible human carcinogen*)."[377] No citations (including to IARC, presumably the source of the listed classifications) were provided for any of the discussion regarding the carcinogenicity of metals, and thus the extent of Dr. Carson's review, analysis or assessment of the metals is unknown.

The extent to which literature was critically reviewed by Dr. Carson is suspect given his incorrect summary that "[IARC] concluded that talcum powder is a 'possible human carcinogen' (Group 2B) when applied to the perineum, **meaning that there is *insufficient* evidence of carcinogenesis in humans, but *strong evidence* in other mammalian species** [emphasis

[374] Expert Report of Laura Plunkett, PhD, DABT, 11/16/18, p. 7.
[375] Deposition of Laura Plunkett, PhD, DABT, 12/19/18, 157:1-158:6.
[376] Deposition of Laura Plunkett, PhD, DABT, 12/19/18, 158:6-10.
[377] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6.

added]."[378] Dr. Carson's summary, while correct for some IARC Group 2B carcinogens (see Table 2 on page 13), was completely wrong for IARC's conclusion regarding talc not containing asbestos or asbestiform fibers (i.e., ***limited*** **evidence in humans and** ***limited*** **evidence in animals**).[379]

Dr. Carson stated that he "performed a risk assessment and considered whether perineal use of those products poses a safety risk to consumers."[380] However, his conclusions lack any estimate of risk (the probability ovarian cancer will occur for any given level of exposure) and his dose-response discussion is esoteric and lacks any numerical parameters (e.g., what doses are associated with effects?). As described on page 9, a human health risk assessment is performed according to four basic steps, of which dose is a key parameter. Without an analysis of the nature and magnitude of doses associated with human risk, Dr. Carson relies on hazard identification alone for his "risk assessment." As stated above, use of hazard identification statements alone to draw conclusions regarding risk does not constitute a human health risk assessment; use of hazard identification alone is methodologically flawed and not consistent with methods generally accepted by toxicologists.

iv) Dr. Plunkett's grouping of all chemicals with carcinogenic hazards together is not consistent with generally accepted methods used by toxicologists.

Dr. Plunkett's following assertion regarding toxicology of mixtures was not consistent with general toxicological principles: "*When considered together with general principles of toxicology, the available data relating to mechanism of carcinogenicity of talcum powder products, where the body powders are a mixture of compounds with carcinogenic hazard, indicate that the various compounds in talcum powder products would be expected to produce at least an additive effect on the risk of cancer based on their ability to induce similar biological responses that underl[ie] carcinogenesis (Eaton, D.L. and S.G. Gilbert. 2013. Principles of toxicology. In: Casarett & Doull's Toxicology: The Basic Science of Poisons, 8th edition. Klaassen, C.D. (ed.). McGraw-Hill: New York: NY. Chapter 2, pp. 19-20; EPA, 2000).*"[381] The Casarett & Doull's Toxicology textbook Dr. Plunkett cites includes multiple possibilities for the response following multiple chemicals (with carcinogenic hazards) given simultaneously, including "antagonism," which occurs when co-administered chemicals interfere with each other's action and the overall response is less than either induces separately. It is scientifically invalid to speculate regarding anticipated effects of mixtures without extensive research (or experimentation).

[378] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 4.
[379] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.
[380] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 11.
[381] Expert Report of Laura M. Plunkett, PhD, DABT, 11/16/18, p. 47.

v) Dr. Crowley's assertion that effects from fragrance ingredients are likely additive to the alleged risks of talc is not consistent with generally accepted methods used by toxicologists.

Dr. Crowley testifies: "*Another consideration is, you know, the safety studies are usually single ingredient safety studies. So, you know, if we were to do a safety study of para-Cresol in an animal, it would be simply that. It wouldn't be para-Cresol and another 142 other chemicals. Right? So very likely there's additive effects.*" Dr. Crowley's assumption about chemical mixtures is not based on generally-accepted scientific methodology. The toxicology of mixtures is complex and additivity cannot be assumed. The *Casarett & Doull's Toxicology* textbook includes multiple possibilities for the response following multiple chemicals (with carcinogenic hazards) given simultaneously, including "antagonism," which occurs when co-administered chemicals interfere with each other's action and the overall response is less than either induces separately.[382] It is scientifically invalid to speculate regarding anticipated effects of mixtures without extensive research (or experimentation).

vi) Dr. Zelikoff's method for assessing biological plausibility is scientifically flawed and not a generally accepted scientific methodology.

As described in the specific metals sections above (beginning on pages 54, 61 and 67), Dr. Zelikoff provides general information for hazard identification for potential cancer effects in various tissues (not including the ovary). However, the assessment is done without regard to the levels of exposure (or concentrations) needed for increased risk to human health. In this matter, Dr. Zelikoff's reliance on hazard statements alone is not scientifically supported given the innocuous background concentrations to which all humans are exposed without associated ovarian cancer risk and the absence of any identified risk of ovarian cancer identified in any epidemiological or animal study. Dr. Zelikoff's reliance on hazard identification alone, without consideration of the levels of exposure necessary for the hazard to pose a cancer risk, is not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

vii) Multiple plaintiffs' experts omit the use of Bradford Hill causation criteria or apply the criteria without critical review in a manner not consistent with generally accepted methods.

The Bradford Hill criteria for causation are critical to the first methodological step (hazard identification) toxicologists perform during human health risk assessments (see discussion beginning on page 9).[383]

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[382] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019. p. 31.

[383] National Research Council. Risk Assessment in the Federal Government – Managing the Process. Washington DC: National Academy Press. 1983; US EPA. Guidelines for Carcinogen Risk Assessment. Washington, DC. Report No.: EPA/630/P-03/001F. March, 2005.

Many of the plaintiffs' experts (Drs. Crowley, Plunkett and Zelikoff) did not include a causation analysis as a basis for their opinions.[384] Because they lack an affirmative causation analysis, which is a necessary component of any risk assessment analysis, their conclusions regarding the risk of ovarian cancer are scientifically invalid.

Dr. Carson performed a Bradford Hill causation analysis in his assessment, but his lack of critical review renders the assessment methodologically flawed and unreliable.[385] His discussion is a shallow account of asserted arguments made in favor of a potential association/causation between perineal talc use and ovarian cancer. Additionally, his literature citations are limited to lists of citations (e.g., author, date) purportedly supportive of his opinion, but lack any information regarding the extent of analysis required to inform his opinions.

- For example, under the epidemiology heading of "what evidence links exposure to talcum powder products with ovarian cancer," Dr. Carson includes the following statement: "*Multiple epidemiological studies have examined the link between the personal hygiene use of talc containing products and the occurrence of ovarian cancers (Booth M, 1989) (Cook LS K. M., 1997) (Cook LS e. a., 1997) (Cramer DW, 1982) (Whittemore AS, 1988) (Harlow BL W. B., 1989) (Chen Y, 1992) (Harlow BL C. D., 1992) (Rosenblatt KA, 1992) (Hartge P, 1988) (Tzonou A, 1993) (Chang S, 1997) (Heller DS, 1996) (Penninkilampi R, 2018).*"[386] No information is given regarding how Dr. Carson selected the listed studies; no statement is provided as to whether the listed studies support or contradict the association; and there is no explanation regarding any details of the studies.

  Upon closer examination of these citations, it is apparent that three of the listed citations were not unique publications that pertain to the heading question regarding epidemiology: the two Cook references from 1997 include an original publication and an erratum; "Heller, DS 1996"[387] is not an epidemiology study of talc and ovarian cancer; and "Hartge P, 1988" is not listed in the literature section of the report, and therefore could not be verified.

Of the remaining citations, "Penninkilampi R, 2018,"[388] was a meta-analysis and the 10 remaining citations were unique case-control studies (listed among the 30 case-control studies in Table 5, beginning of page 22 of this report). The authors failed to find a statistically significant association between perineal talc use and ovarian cancer in six of the 10 studies cited by Dr. Carson. Because Dr. Carson did not consider the nature and magnitude of the associations

[384] Depostiton of Michael Crowley, PhD, 1/4/19, 123:16-20, 123:22-124:1; Deposition of Laura Plunkett, PhD, DABT, 12/19/18, 34:7-21; Deposition of Judith Zelikoff, 1/21/10, 73:8-16, 201:24-202:8. Expert Report of Michael M. Crowley, PhD, 11/12/18; Expert Report of Laura M. Plunkett, PhD, DABT, 11/16/18; Expert Report of Judith Zelikoff, PhD, 11/16/18.
[385] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 5-6.
[386] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 6.
[387] Heller, D.S., Westhoff, C., Gordon, R.E. and Katz, N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol. 174(5):1507-10, 1996.
[388] Penninkilampi, R. and Eslick, G.D. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. Epidemiology Epidemiology. 29(1):41-49, 2018.

observed in the studies, his report is potentially misleading and his analysis is not consistent with generally accepted scientific methodology.

- Dr. Carson also provided an incorrect summarization of IARC conclusions. Specifically, Dr. Carson wrote that "*[IARC] concluded that talcum powder is a 'possible human carcinogen' (Group 2B) when applied to the perineum,* ***meaning that there is insufficient evidence of carcinogenesis in humans, but strong evidence in other mammalian species*** [emphasis added]."[389] Dr. Carson's summary, while correct for some IARC Group 2B carcinogens (see Table 2 on page 13), was completely incorrect for IARC's conclusion regarding talc not containing asbestos or asbestiform fibers. IARC in fact found ***limited*** **evidence of carcinogenesis in humans and** ***limited*** **evidence of carcinogenesis in animals**.[390]
- Another example of Dr. Carson's insufficient analysis was included in the previous opinion: *Because Dr. Carson did not consider the nature and magnitude of doses associated with human risk, his analysis is not consistent with generally accepted scientific methodology* (beginning on page 83).

b. Science-based concerns

i) Opinions by some of plaintiffs' experts that any exposure to a carcinogen can cause cancer are not consistent with generally accepted methods used by toxicologists to analyze and assess risk to human health.

A number of plaintiffs' experts, including Dr. Crowley, take the position that it would suffice to establish that talcum powder or its alleged constituents are carcinogenic because any exposure to a carcinogen can cause cancer, but this position lacks scientific support. Carcinogens exist everywhere. All of us are exposed to natural and synthetic carcinogenic substances in our daily lives. Dose is the key to whether or not a carcinogen poses a risk to human health.[391] U.S. regulatory agencies explicitly recognize that the degree of cancer risk to humans rests, in part, on dose, and that risk cannot be properly evaluated or understood without an appreciation of dose. Consistent with this recognition, these agencies establish acceptable levels of human exposure to carcinogens, and thereby establish acceptable human doses of carcinogens, whereby the "acceptability" of the dose is predicated on the degree of anticipated risk.[392]

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[389] Expert Report of Arch Carson, MD, PhD, 11/16/18, p. 4.
[390] IARC. Carbon Black, Titanium Dioxide, and Talc. In: Volume 93 - Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans. Lyon: World Health Organization; 2010.
[391] Ames, B. and Gold, L.S. Holiday Dinner Menu. New York: American Council on Science and Health (ACSH), 2004; Ames, B.N. and Gold, L.S. Too many rodent carcinogens: mitogenesis increases mutagenesis. Science, 249(4972):970-971, 1990; Borowska, S. and Brzóska, M.M. Metals in cosmetics: implications for human health. J Appl Toxicol., 35(6):551-72, 2015; Brambilla, G., et al. Update of carcinogenicity studies in animals and humans of 535 marketed pharmaceuticals. Mutat Res., 750(1):1-51, 2012; Gribble, G.W. Food chemistry and chemophobia. Food Security, 5(2):177-187, 2013; National Toxicology Program. 13th Annual Report on Carcinogens. US Department of Health and Human Services, Public Health Service, Research Triangle Park, 2014.
[392] National Research Council. Risk Assessment in the Federal Government - Managing the Process. Washington DC: National Academy Press, 1983; National Research Council. Science and Decisions. Advancing Risk Assessment. Washington DC: The National Academies Press, 2009; US EPA. Risk assessment for carcinogens.

ii) Dr. Crowley's opinion that positive genotoxicity assays (specifically CHO assays) provide an animal model of support for increased risk of ovarian cancer is not consistent with generally accepted methods used by toxicologists.

Associations between DNA alterations and potential carcinogenic outcomes have been well established, and tests established a half-century ago are still used today. For example, the relatively rapid and inexpensive "Ames Assays," developed in the 1970s, were some of the first tests to characterize compounds (or their metabolic products) as mutagens and potential carcinogens. However, the Ames test is done using bacteria, which leads to uncertain results in animals (and humans) due to different bacterial biology (especially activation and detoxification mechanisms), genome organization, and DNA repair mechanisms (i.e., would mammalian cells react the same as bacterial cells?).[393] Scientists recognized the need for mutagenesis assays to be biologically closer to humans while still being less costly and cumbersome than long-term animal tests. They looked to cultured animal and human cell models to fulfill this role. Early efforts to use mammalian cells resulted in more complicated, multistep procedures compared to procedures for testing mutagenicity in bacteria. Different mammalian cell types were evaluated for use in mutagenicity assays.

One of these cell types was Chinese hamster ovary fibroblast (CHO) cell lines, which were initially selected because in the mid-1970s they were the best-characterized mammalian cells, exhibited high cloning efficiency (almost every cell would divide into two subsequent cells), and they replicated relatively quickly.[394] Advances in *in vitro* techniques for CHO cells to increase growth robustness were coupled with development of chromosomal aberration and mutation assays[395] to create standard assays that would become part of the battery of genotoxicity assays used over subsequent decades and continuing in use today.[396]

[updated February 5, 2016]. Available from: https://www.epa.gov/fera/risk-assessment-carcinogens [Accessed on 8/15/2016], 2016.

[393] Howard-Flanders, P. Mutagenesis in mammalian cells. Mutation Research/Reviews in Genetic Toxicology. 86(3):307-27, 1981; Li, A.P. Simplification of the CHO/HGPRT mutation assay through the growth of Chinese hamster ovary cells as unattached cultures. Mutation Research/Environmental Mutagenesis and Related Subjects. 85(3):165-75, 1981.

[394] Hsie, A.W., Couch, D.B., O'Neill, J.P., *et al.* Utilization of a quantitative mammalian cell mutation system, CHO/HGPRT, in experimental mutagenesis and genetic toxicology. Presented at: Chemical industry institute of toxicology workshop on strategies for short-term testing for Mutagens/Carcinogens, Research Triangle Park, North Carolina, USA, 11 Aug 1977; 1977; Hsie, A.W., Casciano, D.A., Couch, D.B., *et al.* The use of Chinese hamster ovary cells to quantify specific locus mutation and to determine mutagenicity of chemicals. A report of the gene-tox program. Mutat Res. 86(2):193-214, 1981; Li, A.P. Simplification of the CHO/HGPRT mutation assay through the growth of Chinese hamster ovary cells as unattached cultures. Mutation Research/Environmental Mutagenesis and Related Subjects. 85(3):165-75, 1981.

[395] The CHO mutation assay is a forward mutation assay because the assay outcome counts cells that have "gained function" through mutation. The basis for the test is the genome of CHO cells, which contains one functional copy of the HPRT gene; when the cells are exposed to mutagenic compounds, the HPRT gene is affected and the cells will no longer produce functional HPRT. When CHO cells are exposed to 6TG (6-thioguanine), functional HPRT metabolizes TG into a toxic metabolite and prevents normal replication. Mutations in the HPRT gene prevent formation of a toxic metabolite and allow for normal growth of the CHO cells. The increased number of cell colonies following the test article and TG treatment corresponds to the test article's mutagenicity. (Hsie, A.W., Casciano, D.A., Couch, D.B., *et al.* The use of Chinese hamster ovary cells to quantify specific locus mutation and

Dr. Crowley's opinions depend too heavily on the findings of studies that use CHO cell lines. In his deposition of January 4, 2019, Dr. Crowley testified as follows: "*[Q.] …You are not aware of any epidemiologic studies that associate the fragrance chemicals or the chemicals that you identified in Shower to Shower or baby powder with an increased risk of ovarian cancer. Correct? … A. I mean, you keep tagging on the "in human" part of it. I mean, we have animal studies that show toxicity issues with cells in animal models, like Chinese hamster ovary cell models, oocyte degeneration that are associated with female reproductive organs. So, no, not in humans, but we've seen in vitro and in vivo animal studies.*"[397] When later asked if d-limonene is a genotoxic material, Dr. Crowley states: "*I don't believe it's been classified as that, but cytotoxicity against Chinese Hamster ovary cells indicates that it could be against ovaries, at least in this animal model*."[398]

Dr. Crowley's testimony misrepresents the purpose of using the Chinese hamster ovary (CHO) cells in genetic or mutagenicity testing. CHO cells are used because, as described above, they are easy to work with and are part of well-validated genotoxicity assays. Many specific tissues and cell lines are used for genotoxicity testing for this reason, including mouse lymphoma cells, human peripheral blood lymphocytes, and Syrian hamster embryo cells. The cells used for testing represent well-validated models designed to detect genetic changes, but they in no way represent the target tissue of the chemical being tested. Dr. Crowley's suggestion that a positive result from an assay using CHO cells suggests specific risk for ovarian cancer is completely unfounded.

Dr. Crowley testified that he had not found any publications that link the fragrance chemicals in baby powder and Shower to Shower to ovarian cancer in humans; however, he claimed that positive genotoxicity assays (specifically CHO assays, largely) supported his claim of ovarian cancer in animal models.[399] A single positive test in the CHO assay is not sufficient to conclude genotoxicity. The current genotoxicity testing guidance provided by the ICH recommends a standard test battery that includes bacterial, *in vitro* and *in vivo* testing. However, the guidance notes that "*comparative trials have shown conclusively that each in vitro test system generates both false negative and false positive results in relation to predicting rodent carcinogenicity*."[400] Under this guidance, a positive *in vitro* mammalian cell assay (e.g.,

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to determine mutagenicity of chemicals. A report of the gene-tox program. Mutat Res. 86(2):193-214, 1981; Oberly, T.J., Bewsey, B.J. and Probst, G.S. A procedure for the CHO/HGPRT mutation assay involving treatment of cells in suspension culture and selection of mutants in soft-agar. Mutation Research/Environmental Mutagenesis and Related Subjects. 182(2):99-111, 1987.)

[396] Li, A.P., Aaron, C.S., Auletta, A.E., *et al.* An evaluation of the roles of mammalian cell mutation assays in the testing of chemical genotoxicity. Regulatory Toxicology and Pharmacology. 14(1):24-40, 1991; International Programme on Chemical Safety (IPCS). Environmental Health Criteria 240: Principles and methods for the risk assessment of chemicals in food. Geneva: World Health Organization. 2009.

[397] Deposition of Michael Crowley, PhD, 1/4/19, 217:12-218:4.

[398] Deposition of Michael Crowley, PhD, 1/4/19, 221:20-222:4.

[399] Deposition of Michael Crowley, PhD, 1/4/19, 114:9-119:11.

[400] ICH. Guidance on Genotoxicity Testing and Data Interpretation For Pharmaceuticals Intended for Human Use S2(R1). November 9, 2011.

CHO cell assay) that also results in clearly negative results in two well conducted, tissue-appropriate *in vivo* assays is considered sufficient evidence for lack of genotoxic potential *in vivo*.[401]

It is widely understood that a single positive genotoxicity test is not the basis for labeling a chemical genotoxic. In 2005, The International Workshop on Genotoxicity Testing (IWGT) convened its Expert Working Group on Hazard Identification and Risk Assessment in Relation to In Vitro Testing to develop strategies for appropriate interpretation and follow-up testing when initial *in vitro* tests are positive. The group noted the "*high frequency of positive in vitro findings in the genotoxicity test batteries with agents found not to be carcinogenic and thought not to pose a carcinogenic health hazard to humans.*"[402] Even when a single test result is clearly positive, the Working Group emphasized the importance of considering the relevance to human health, including how the result compares to other assays for the same endpoint, whether the mode or mechanism of action is relevant to humans, and whether the genotoxic effect observed is likely to occur *in vivo* at concentrations expected as a result of human exposure.

Thresholds for genotoxic compounds

The textbook, *Casarett & Doull's Toxicology*, is recognized as one of the most widely used and fundamental textbooks on toxicology. The most recent edition describes the scientific knowledge of a threshold (a concentration below which the probability of an individual responding is zero) for DNA-damaging agents. Specifically, the last two decades of research brought advancements in analytical approaches, more sensitive methodologies and knowledge regarding biological mechanisms of genetic toxicology. With these scientific advances, knowledge has been gained regarding the complex interactions within intrinsic DNA repair pathways and interplay between different DNA repair and DNA damage response pathways. These processes neutralize the effects of ever-present background DNA damage and sufficiently counteract mutations at low exposures to genotoxic compounds/agents.[403]

Of note, the historical hypothesis – that the dose-response curve for genotoxic compounds (compounds capable of altering DNA) did not include a threshold below which effects were not observed – relies on the assumption that every exposure, no matter how small, contributed a risk for disease. Two key factors have refuted this hypothesis:

1. Scientific data have never demonstrated that a single molecule is capable of causing disease; and

2. Scientific data have been published that refute the hypothesis, including:

[401] ICH. Guidance on Genotoxicity Testing and Data Interpretation For Pharmaceuticals Intended for Human Use S2(R1). November 9, 2011.
[402] Thybaud, V., Aardema, M., Clements, J., *et al.* Strategy for genotoxicity testing: hazard identification and risk assessment in relation to in vitro testing. Mutat Res. 627(1):41-58, 2007.
[403] Klaassen, C.D. Casarett and Doull's Toxicology: The Basic Science of Poisons. 9th ed. New York: McGraw-Hill. 2019.

- The recent IWGT report pointed out the shortcomings of relying on genotoxicity screening assays for predicting carcinogenicity, indicating: "*it is clear that cellular exposures attained in* in vitro *assays often greatly exceed those achievable* in vivo *and potentially lead to toxicity and cellular disturbances that cause genetic damage that would not occur under conditions more reflective of actual* in vivo *exposures*" and

  "*it has become recognized that qualitative outcomes of in vitro genotoxicity tests do not adequately correspond to the outcomes of rodent carcinogenicity bioassays or with in vivo genotoxicity*."[404]

- Practical thresholds for DNA-reactive genotoxic carcinogens have been demonstrated in both animal[405] and *in vitro*[406] studies.

  A recent review of the scientific dataset regarding cobalt concluded that cobalt particles should be considered genotoxic carcinogens with a practical threshold. This was based on the attribution of tumor formation on generation of reactive oxygen species, a non-stochastic mechanism in nature and therefore expected to exhibit a threshold.[407]

Plaintiffs' expert Dr. Crowley's approach regarding the inapplicability of dose toward genotoxicity is outdated and not supported by current science. He testified that "*genotoxic materials do not – are not thresholded [sic]. They don't have a threshold. One molecule is enough to cause an increased risk*";[408] "*As I told you earlier, genotoxic materials do not live under a dose response relationship. If it's been classified as genotoxic, one molecule is enough to cause an increase in risk associated with that particular compound*";[409] and "*Genotoxins don't have a threshold.*"[410] Dr. Crowley's testimony claiming genotoxic compounds do not have a threshold and "one molecule is enough" is not supported by the current toxicological knowledge, as scientific data have never demonstrated that a single molecule is capable of causing disease and scientific data have been published that refute the hypothesis that a single molecule is capable of causing disease.

[404] MacGregor, J.T., Frötschl, R., White, P.A., *et al.* IWGT report on quantitative approaches to genotoxicity risk assessment I. Methods and metrics for defining exposure–response relationships and points of departure (PoDs). Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 783:55-65, 2015.
[405] Fukushima, S., Wei, M., Kakehashi, A. and Wanibuchi, H. Threshold for Genotoxic Carcinogens: The Central Concern in Carcinogenic Risk Assessment. Genes and Environment. 34(4):153-56, 2012.
[406] Jenkins, G.J., Zair, Z., Johnson, G.E. and Doak, S.H. Genotoxic thresholds, DNA repair, and susceptibility in human populations. Toxicology. 278(3):305-10, 2010.
[407] Lison, D., van den Brule, S. and Van Maele-Fabry, G. Cobalt and its compounds: update on genotoxic and carcinogenic activities. Crit Rev Toxicol. 1-18, 2018. DOI: 10.1080/10408444.2018.1491023.
[408] Depostiton of Michael Crowley, PhD, 1/4/19, 124:14-20, 125:15-23.
[409] Depostiton of Michael Crowley, PhD, 1/4/19, 131:20-132:3.
[410] Depostiton of Michael Crowley, PhD, 1/4/19, 204:7.

iii) Dr. Crowley misrepresented both study outcome and the FDA's ruling in his statement regarding benzophenone.

Dr. Crowley was incorrect in his statement that: "*Benzophenone was recently removed from use in foods by FDA due to histiocytic sarcoma observed in ovaries and uterus, higher incidences of kidney tumors and leukemia in animal studies, and* in vivo *estrogenic activity [emphasis added]*."[411]

According to the *Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. Final Rule* (the reference cited by Dr. Crowley), the FDA concluded:

> *"Based on results from the NTP studies, FDA concluded that, under the conditions of the 2-year NTP bioassays, benzophenone induced renal tubular tumors in male rats and hepatocellular tumors in male mice"*

Although the FDA was amending the food additive regulations to no longer authorize the use of benzophenone [because it induces cancer in laboratory animals], after its weight-of-evidence analysis, it "*concluded that benzophenone is unlikely to induce tumors in humans at current use levels as a synthetic flavoring substance and adjuvant in food*." The FDA also wrote: "*Despite FDA's scientific analysis and determination that these substances do not pose a risk to public health under the conditions of their intended use, under the Delaney Clause this finding of carcinogenicity renders the additives 'unsafe' as a matter of law and FDA is compelled to amend the authorizations for these substances as food additives to no longer provide for the use of these synthetic flavoring substances.*"[412]

Dr. Crowley testified: "*Some female mice also developed rare histiocytic sarcomas. I believe those were associated with the repro- -- female reproductive organs*."[413] However, histiocytic sarcomas are in fact rare, hematopoietic tumors (i.e., they originate from blood cells) that were observed in two mid-dose and five high-dose female mice (observations of ovarian and uterine involvement occurred only in the high-dose females). The study authors characterized them as follows: "*the histiocytic sarcomas were highly invasive. Multiple organs throughout the body had neoplastic histiocytic lesions*." These organs included ovarian and uterine tissue, as well as spleen, adrenal gland, kidney, urinary, bladder and multiple lymph nodes.[414] Observation of an invasive, hematopoietic lesion in the ovary does not support the concept that benzophenone causes ovarian cancer.

In short, Dr. Crowley's assertion that the FDA removed benzophenone from use as a food flavoring "*due to histiocytic sarcoma observed in ovaries and uterus [emphasis added]*"

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[411] Expert Report of Michael M. Crowley, PhD, 11/12/18, p. 48, 65.
[412] US FDA. Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. Final rule. 21 CFR Parts 172 and 177. Oct 9. Federal Register. 83(195):50490-503, 2003.
[413] Deposition of Michael Crowley, PhD, 1/4/19, 278:8-11.
[414] Rhodes, M.C., Bucher, J.R., Peckham, J.C., *et al.* Carcinogenesis studies of benzophenone in rats and mice. Food Chem Toxicol. 45(5):843-51, 2007.

misrepresents both the science (by intentionally omitting the pervasiveness of the cancer of hematopoietic origin) and the details of the FDA's ruling on benzophenone.

iv) Methods used by Dr. Saed to generate data presented in his report and manuscript were flawed and unreliable and therefore preclude any conclusion regarding the activity of talc with the studied cells.

Deficiencies regarding the methodological study design employed by Dr. Saed make his results scientifically unreliable. As detailed below, a review of Dr. Saed's laboratory notebook and testimony show study design deficiencies for the data presented in his Expert Report[415] and Manuscript.[416] These methodological flaws prevent the use of his results to make any valid scientific conclusion.

- Dr. Saed failed to establish that the colorimetric assays he used (e.g., protein, catalase, MTT assays) remained valid in the presence of talc particles, despite the well-understood possibility that particulate matter can interfere with such assays. Most of Dr. Saed's assays rely on optical density (OD) measurements, which measure the ability of a sample to absorb or block the passage of light (at a specific wavelength).[417] If merely the presence of talc particles affects (i.e., increases) sample OD values, subsequent results would be considered invalid (i.e., "false positives") because the increased OD values would fail to represent the specific outcome of interest (e.g., protein, catalase, MTT).

  Dr. Saed testified that talc was not evaluated as a potential interference because no talc would be present in the extracted proteins. He claimed to know talc would not be in the extracted proteins because in the process of extracting proteins, "*you wash off all the media, you precipitate the cells, you lyse the cells, you extract proteins*."[418] He later testified that he knew talc particles were not carried with the extracted proteins because the standard method was established "from 1960" to only extract proteins from cells.[419] Despite Dr. Saed's no-talc claim, no analysis was done to evaluate the extent to which talc may have been extracted with proteins. Such extraction of talc is a possibility because proteins are concentrated from cellular contents using centrifugation – which also would concentrate any talc particles in the cytoplasm of cells or settled/adhered to cell surfaces and/or plastic well surfaces due to lipophilic forces – meaning that aqueous washing would not ensure that talc was separated entirely from the proteins on extraction. The scientific community recognizes the complications posed by particles (which are difficult to rinse off and can be centrifuged and concentrated together with proteins) and

[415] Expert Report of Dr. Ghassan M. Saed, 11/16/18.
[416] Dr. Ghassan M. Saed Manuscript, Fletcher, N., Harper, A., Memaj, I., Fan, R., Morris, R., and Saed, G. Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer", submitted to Reproductive Sciences, 1/3/19.
[417] Farlex, Optical Density. In: The Free Dictionary. https://medical-dictionary.thefreedictionary.com/optical+density. Last accessed February 12, 2019.
[418] Deposition of Ghassan M. Saed, 1/23/19, 122:14-21.
[419] Deposition of Dr. Ghassan Saed, 2/14/19, 440:22-441:19.

their potential interference with *in vitro* assays. The propensity of particles to interfere with absorbance (via direct particle absorbance of wavelength of interest, via particle adsorption of indicator compound, or via inactivation of the activating enzyme) led to the conclusion that "*valid particle toxicity assessments can only be assured after first performing controls to verify that the particles under investigation do not interfere with a specific assay at the expected concentrations*."[420] Dr. Saed failed to validate the assays used in his manuscript, further rendering his results flawed and unreliable and incapable of supporting any scientific conclusion about the activity of talc with the studied cells.

- Dr. Saed's results do not correspond with generally accepted methodology used to evaluate potential *in vitro* relationships using multiple biological replicates. Because biology is complex, results from *in vitro* experiments can depend on the unique conditions that vary each time an "experiment" is run (due to differences when cells were plated, treated or some other factor). For this reason, most scientists wait to make any conclusions regarding effects until they observe similar results among triplicate (i.e., three separate) experiments. In this context, an "experiment" starts with plating cells into dishes (i.e., pouring a solution of cells onto a dish and allowing the cells to attach and replicate to a population ready to be treated) and then progresses to treating and evaluating the cells. One well-designed experiment usually includes multiple dishes of control and each treatment dose. That did not happen here; Dr. Saed's experiment plated and treated all cells at one time, and as such, his experiment included only one biological replicate.

  The scientific community recognizes that *in vitro* experiments should be repeated on multiple days because "*it is hard to know what will happen if the experiment is run a second time*."[421] Dr. Saed's experiments included one dish (N=1) per cell type and treatment group.[422] Without duplicate (or triplicate) biological replicates (ideally plated onto tissue culture plates on separate days), the variability in biological response and the potential for spurious correlations are unknown.

  Despite the fact that these principles are well established and straightforward, it appears that Dr. Saed is unaware that he did not conform to them. Figure 1 of Dr. Saed's Reproductive Sciences manuscript states, "*Experiments were performed in triplicate*." This claim is erroneous because, as described below, in his deposition,[423] and the data in his notebook,[424] it appears all data are based on a single experiment (cells were plated one time with individual plates for each treatment and cell type). There are also error bars

[420] Holder, A.L., Goth-Goldstein, R., Lucas, D. and Koshland, C.P. Particle-Induced Artifacts in the MTT and LDH Viability Assays. Chemical Research in Toxicology. 25(9):1885-92, 2012.
[421] Lazic, S.E., Clarke-Williams, C.J. and Munafò, M.R. What exactly is 'N' in cell culture and animal experiments? PLOS Biology. 16(4):e2005282, 2018.
[422] Deposition of Ghassan M. Saed, 1/23/19, 124:15-17.
[423] Deposition of Ghassan M. Saed, 1/23/19, 125:19-126:12.
[424] Ghassan M. Saed Laboratory Notebook, SAED000003.

on the figures that, based on the descriptions of the figures, should be the average of triplicate "experiments," not just multiple analyses of the same sample extract. For example, the notebook graph on SAED000034 appears to be the same graph of data as Figure 1C from his manuscript.[425] Samples were prepared on notebook page numbers SAED000029-30. But the error bars measured the variability in analysis of the same sample three times (SAED000030 has a sample number with a line to cover three circles (or "wells") to presumably indicate that aliquots of the same sample were repeatedly added to three different cells and subsequently analyzed). The error bar represented the variability in adding and analyzing the same sample three times in three different wells, which, as a scientific matter, is not "three experiments." It is one experiment.

Dr. Saed testified that his interpretation of the word "triplicate" was that optical density (e.g., for catalase measurement) from a single sample (cells grown and treated in one petri dish) was measured (analyzed) three times.[426] This explanation betrays a fundamental lack of understanding as to what it means to conduct an experiment in triplicate. To illustrate the error in Dr. Saed's logic, it is as if he claimed to have analyzed the average body weight of a 21-year old, 6'1" male by measuring one man's weight three times – which is obviously very different than an average body weight of three different 21-year old, 6'1" men. The latter measurement includes biological variability, while the former assesses only technical variability of the measuring equipment or technique. Because results from *in vitro* experiments can depend on the unique conditions that vary each time an experiment is run, it is inaccurate to merely perform technical replicates of single biological samples and denote results as performing multiple experiments. Without duplicate (or triplicate) biological replicates (ideally plated onto tissue culture plates on separate days), the variability in biological response and the potential for spurious correlations are unknown. Dr. Saed's results from a single experiment are methodologically flawed, unreliable, and provide no value toward a conclusion regarding the activity of talc with the studied cells.

- Dr. Saed's uncertain and conflicting testimony and documentation concerning the amount of DMSO used in his control dishes further renders his results unreliable. From documentation in the notebook, Dr. Saed's single experiment (described in the previous bullet) was based on different amounts of a talc/DMSO solution added to studied cells. The notebook includes a task entitled: "*need dose for treatment with talc Unt (untreated), 5, 20 and 100 µg/mL.*"[427] Subsequently calculations were provided to determine the volume of a 10,000 µg/mL stock solution of talc in DMSO (not 50,000 µg/mL, as specified in Dr. Saed's accepted manuscript) to add to 5 mL of cell medium in each dish

[425] Dr. Ghassan M. Saed Manuscript, Fletcher, N., Harper, A., Memaj, I., Fan, R., Morris, R., and Saed, G. Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer", submitted to Reproductive Sciences, 1/3/19.
[426] Deposition of Ghassan M. Saed, 1/23/19, 123:1-124:4.
[427] Ghassan M. Saed Laboratory Notebook, SAED000003; Deposition of Dr. Ghassan Saed, 2/14/19, 443:15-21.

(i.e., 2.5, 10 and 50 µL) to create final concentrations of 5, 20 and 100 µg/mL, respectively.[428] No documentation is provided for the control dishes beyond the "Unt" (untreated) denotation – there is no record of the addition of any DMSO to the control dish for each cell type tested (as specified above, there was one control dish for each cell type tested).[429] Dr. Saed initially testified 2.5, 10 and 50 µL of DMSO alone was added to the corresponding controls;[430] however, addition of multiple, different amounts of DMSO to a single dish is nonsensical as only one volume of DMSO is added to each control dish, and there was only one control dish per cell type.[431] The volume of DMSO added to the untreated controls does not appear to be documented in the notebook and Dr. Saed's testimony does not clarify what was actually done. The notebook data reflect that DMSO was added at levels proportional to talc;[432] therefore any impurity in DMSO (or DMSO alone) could have induced effects falsely attributed to talc.

During his second deposition, Dr. Saed's testimony explaining that plates were treated with different concentrations of talc in a set volume of DMSO conflicted with data documented in his laboratory notebook and his previous testimony describing his technique. He now testified that he added the same volume (i.e., 50 µL) of DMSO solutions (with none or successively larger concentrations of talc) to the control and each of the three treated plates.[433]

Generally recognized scientific practice is to rely on data that was documented at the time an experiment was conducted; therefore, the technique of adding successively larger amounts of DMSO-talc solutions to treatment flasks described in Dr. Saed's notebooks must be considered the technique performed for the samples. Dr. Saed's results incorporating different treatment volumes of DMSO that were proportional to talc and unknown/unclear treatment of controls from a single biological experiment are methodologically flawed and unreliable. As a result, they cannot provide valid information regarding the activity of talc with the studied cells.

[428] Ghassan M. Saed Laboratory Notebook, SAED000003-4; Dr. Ghassan M. Saed Manuscript, Fletcher, N., Harper, A., Memaj, I., Fan, R., Morris, R., and Saed, G. Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer", submitted to Reproductive Sciences, 1/3/19.
[429] Ghassan M. Saed Laboratory Notebook, SAED000003-4.
[430] Deposition of Ghassan M. Saed, 1/23/19, 119:3-10.
[431] Deposition of Dr. Ghassan Saed, 2/14/19, 444:3-8.
[432] Ghassan M. Saed Laboratory Notebook, SAED000003-4; Dr. Ghassan M. Saed Manuscript, Fletcher, N., Harper, A., Memaj, I., Fan, R., Morris, R., and Saed, G. Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer", submitted to Reproductive Sciences, 1/3/19.
[433] Deposition of Dr. Ghassan Saed, 2/14/19, 445:6-20.

c. Literature-based concerns

i) Dr. Zelikoff's use of data of unknown quality to inform her opinions is methodologically flawed and not generally accepted by the scientific community.

Dr. Zelikoff used data of unknown quality to inform her opinions regarding the alleged propensity of talc to increase the pro-oxidant state of ovarian cells. As detailed below, her use of a series of abstracts provides no basis for a scientifically valid conclusion.

The scientific community prevents "reliance on data that cannot be replicated or even explained"[434] through established processes to scientifically scrutinize datasets for categorization of the strength of resulting data.[435]

Dr. Zelikoff's opinions rely on a series of citations for abstracts that are of unknown reliability and reproducibility (all were from the same laboratory):

- "Fletcher, 2018 (abstract)" and Fletcher (2018) [436]: **Abstract** for poster presentation Fletcher, Nicole, Ira Memaj, and Ghassan M Saed. "Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells." Reproductive Sciences 25, Supplement 1 (March 2018): 214A-215A.
- "Saed, 2018"[437]: **Abstract** for a poster presentation
  Saed, Ghassan M., Ph.D. "LB-044 - Talcum Powder Enhances Cancer Antigen 125 Levels in Ovarian Cancer Cells and in Normal Ovarian Epithelial Cells." (March 10, 2018).
- "Harper and Saed, 2018" [citation not included in material and data considered list], report text indicates "in a recently accepted **abstract**]"[438]
- "Fletcher and Saed, 2018":[439] [citation not included in material and data considered list. Unclear if citation intent was to Fletcher, 2018 listed above]

Scientifically accepted descriptors of study and data quality can be categorized as follows: "reliable without restrictions;" "reliable with restrictions;" "not reliable;" or "not assignable;" studies for which quality is "not assignable" (and of unknown reliability) include those listed as abstracts or secondary literature (books, reviews, etc.).[440] Dr. Zelikoff's references (listed above) fall into the "not assignable" category. Published abstracts like those relied on by

[434] Walker, V.R. Risk Characterization and the Weight of Evidence: Adapting Gatekeeping Concepts from the Courts. Risk Analysis. 16(6):793-99, 1996.
[435] Klimisch, H.J., Andreae, M. and Tillmann, U. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol. 25(1):1-5, 1997; Rhomberg, L.R., Goodman, J.E., Bailey, L.A., *et al.* A survey of frameworks for best practices in weight-of-evidence analyses. Crit Rev Toxicol. 43(9):753-84, 2013.
[436] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 25.
[437] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 25.
[438] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 25.
[439] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 26.
[440] Klimisch, H.J., Andreae, M. and Tillmann, U. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol. 25(1):1-5, 1997.

Dr. Zelikoff are of unknown reliability due to insufficient information regarding study design, methodology, and interpretation of results. Dr. Zelikoff's opinions stemming from studies with no scientifically reliable data are of unknown significance. Drawing conclusions without any scientifically reliable data is methodologically flawed and not generally accepted by the scientific community.

ii) Dr. Zelikoff's method of copying hazard-identification statements directly (or with a few word changes) without attribution of the author is not a generally accepted scientific methodology.

Significant portions of Dr. Zelikoff's report are copied from other sources without attribution. For example, a majority of text from the section regarding nickel is the same as (or very similar to) text from a review article published by K.S. Kasprzak et al. (2003), which was not cited by Dr. Zelikoff. Generally accepted methodology does not include copying/paraphrasing references without attribution of the source. Although it is possible that independent investigators settled on the same (or very similar) word choice, a couple of items contradict this possibility. In particular, the final sentence regarding routes of administration is a word-for-word match with Kasprzak, and ends with the relatively rare route of "intra-articular space" (inter-joint) exposure. Kasprzak provided five (5) references for the paragraph regarding sites of application (one of which was cited by Dr. Zelikoff). Dr. Zelikoff's three (3) references (Denkhaus, 2002 [also cited by Kasprzak]; IARC, 1987; and Zambelli, 2013) do not discuss intra-articular space administration of nickel. The coincidence of word selection combined with the lack of support of the listed references suggest the material was copied from the uncited (Kasprzak et al., 2003) reference.

See Table 11 for additional examples of information copied by Dr. Zelikoff without attribution to the author.

iii) Dr. Zelikoff's method of copying and pasting incomplete information is misleading and not a generally accepted scientific methodology.

Dr. Zelikoff's practice of cutting and pasting incomplete information from studies leads her to misrepresent the original authors' conclusions. For example, when citing the findings of the study by Patierno (1985),[441] she overstates the authors' conclusion:

- Dr. Zelikoff stated: the "authors associate these alterations as an early event in the process of nickel transformation."
- Patierno (1985) states: "**Although the importance of DNA-protein cross-linking to the transforming effect of nickel is unknown**, the consequences of this lesion in terms of DNA replication may contribute to our understanding …The significance of these results in terms of the carcinogenic action of nickel is not known, but these findings may help explain why nickel compounds do not exhibit potent mutagenicity in mammalian

[441] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8.

systems." "Alterations of the normal association of these proteins with DNA by nickel **<u>may be</u> an early event in the nickel transformation** process [emphasis added]."[442]

iv) Dr. Zelikoff's method of copying and pasting presents outdated information as current scientific knowledge and is misleading and not a generally accepted scientific methodology.

Dr. Zelikoff's practice of cutting and pasting leads her to omit recently-published data. For example, her report lists all IARC classifications of carcinogenicity for nickel through 1990,[443] but fails to include the most recent monograph publication for nickel (2012).[444] Omission of the most recent citation is consistent with copying information from an earlier publication (or failure to conduct a comprehensive literature review).

v) Dr. Levy's method of copying scientific concepts directly (or with a few word changes) without attribution of the author is not a generally accepted scientific methodology.

As summarized in Table 12, portions of Dr. Levy's report are copied directly (or with a few word changes) without attribution to the source of the information. Generally accepted methodology does not include copying/paraphrasing references without attribution of the source.

vi) Inclusion of remarkably similar report text by Drs. Levy and Zelikoff suggests the scientific concepts were copied directly (or with a few word changes) without attribution of the author, which is not a generally accepted scientific methodology.

As specified above, portions of expert reports by Drs. Levy and Zelikoff were directly copied (or copied with a few word changes) without attribution to the source of the information. Comparison of their reports also revealed a section of remarkable similarity (see Table 13), which suggests the information was copied from the same (unknown) source. Generally accepted methodology does not include copying/paraphrasing references without attribution of the source.

[442] Patierno, S.R., Sugiyama, M., Basilion, J.P. and Costa, M. Preferential DNA-protein cross-linking by NiCl 2 in magnesium-insoluble regions of fractionated Chinese hamster ovary cell chromatin. Cancer research. 45(11 Part 2):5787-94, 1985.
[443] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8.
[444] IARC. Nickel and Nickel Compounds. In: Volume 100C - Arsenic, Metals, Fibers, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2012. p. 169-218.

Table 11: Dr. Zelikoff copied much background information without attribution to the author:

"Nickel is classified by IARC as a human carcinogen (Group 1) (IARC, 1973, 1976, 1979, 1982, 1987, 1990). The exact mechanisms of nickel-induced carcinogenesis are not known, but likely involve genetic and epigenetic routes. Nickel (II)-induced genotoxicity may be aggravated through the generation of DNA-damaging reactive oxygen species (ROS) and the inhibition of DNA repair by this metal. Nickel exposure also causes a broad spectrum of epigenetic effects. Contact with nickel compounds can cause a variety of adverse effects on human health (Zambelli and Ciurli, 2013)."[445]

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Review

Nickel carcinogenesis

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Received 2 June 2003; received in revised form 15 August 2003; accepted 15 August 2003

Abstract

Human exposure to highly nickel-polluted environments, such as those associated with nickel refining, electroplating, and welding, has the potential to produce a variety of pathologic effects. Among them are skin allergies, lung fibrosis, and cancer of the respiratory tract. The exact mechanisms of nickel-induced carcinogenesis are not known and have been the subject of numerous epidemiologic and experimental investigations. These mechanisms are likely to involve genetic and epigenetic routes. The present review provides evidence for the genotoxic and mutagenic activity of Ni(II) particularly at high doses. Such doses are best delivered into the cells by phagocytosis of sparingly soluble nickel-containing dust particles. Ni(II) genotoxicity may be aggravated through the generation of DNA-damaging reactive oxygen species (ROS) and the inhibition of DNA repair by this metal. Broad spectrum of epigenetic effects of nickel includes alteration in gene expression resulting from DNA hypermethylation and histone hypoacetylation, as well as activation or silencing of certain genes and transcription factors, especially those involved in cellular response to hypoxia. The investigations of the pathogenic effects of nickel greatly benefit from the understanding of the chemical basis of Ni(II) interactions with intracellular targets/ligands and oxidants. Many pathogenic effects of nickel are due to the interference with the metabolism of essential metals such as Fe(II), Mn(II), Ca(II), Zn(II), or Mg(II). Research in this field allows for identification of putative Ni(II) targets relevant to carcinogenesis and prediction of pathogenic effects caused by exposure to nickel. Ultimately, the investigations of nickel carcinogenesis should be aimed at the development of treatments that would inhibit or prevent Ni(II) interactions with critical target molecules and ions, Fe(II) in particular, and thus avert the respiratory tract cancer and other adverse health effects in nickel workers.

Keywords: Nickel carcinogenesis; Epigenetic toxicity; Genotoxicity; Histones; Hypoxia; Oxidative damage

1. Introduction

Nickel,[1] discovered and named by Cronstedt in 1751, is the 24th element in order of natural abundance in the earth's crust. It is widely distributed in the environment. Natural sources of atmospheric nickel include dusts from volcanic emissions and the weathering of rocks and soils. Natural sources of aqueous nickel derive from biological cycles and solubilization of nickel compounds from soils. Global input of nickel into the human environment is approximately 150,000 metric tonnes per year from natural sources and 180,000 metric tonnes per year from anthropogenic sources, including emissions from fossil fuel consumption, and the industrial production, use, and disposal of nickel compounds and alloys [1,2].

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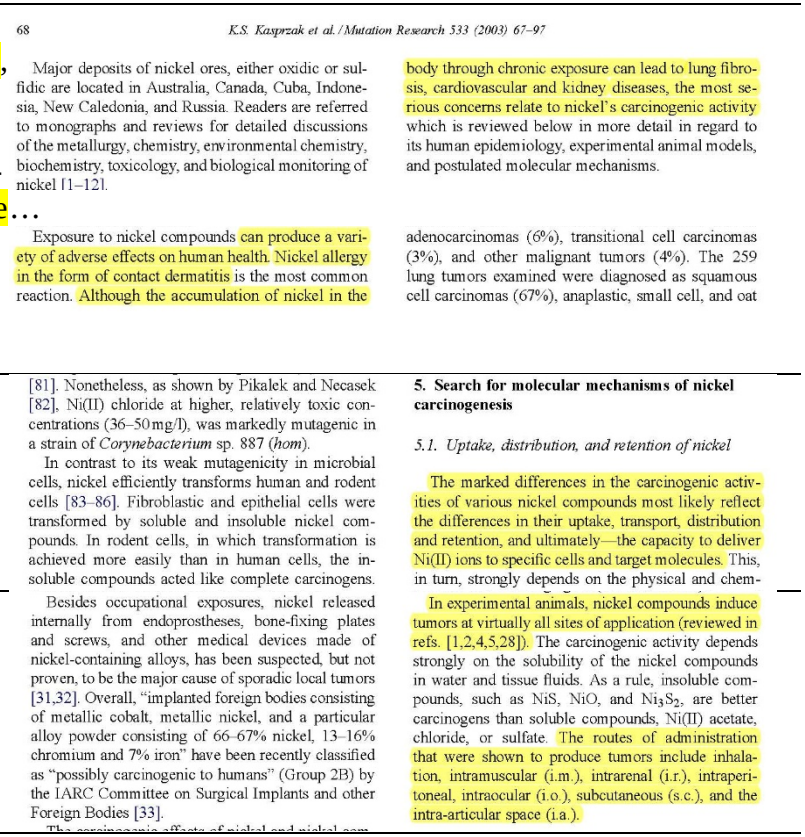
[1] The symbol Ni^{2+} is used to depict free nickel cations only; Ni(II) is used to depict divalent nickel in its compound, e.g., Ni(II) acetate; "nickel" is spelled out if the metal valency is unknown, or irrelevant. Other uncommon abbreviations are explained in the text.

[445] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8; **copied without attribution from:** Kasprzak, K.S., Sunderman, F.W. and Salnikow, K. Nickel carcinogenesis. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 533(1):67-97, 2003. (p. 67).

"Contact with nickel compounds can cause a variety of adverse effects on human health, such as nickel allergy in the form of contact dermatitis, lung fibrosis, cardiovascular and kidney diseases and cancer of the respiratory tract. Chronic non-cancer health effects may result from long-term exposure to relatively low concentrations of pollutants (Duda-Chodak and Blaszcyk, 2008). Although the accumulation of nickel in the body through chronic exposure can lead to a number of diseases, the most serious concerns relate to nickel's carcinogenic activity. Increased risks of malignant tumors, such as nasal and sinusoidal cancers, and cancers of the lung and larynx have been noted (IARC, 1987)."[446]

"The marked differences in the carcinogenic activities of various nickel compounds most likely reflect the differences in their uptake, transport, distribution and retention, and ultimately—the capacity to deliver nickel (II) ions to specific cells and target molecules." [447]

"In experimental animals, nickel compounds induce tumors at virtually all sites of application (Denkhaus, 2002; IARC, 1987; Zabmelli [sic], 2013). The routes of administration that were shown to produce tumors include inhalation, intramuscular, intrarenal, intraperitoneal, intraocular, subcutaneous and the intra-articular space (*Id.*)." [448]



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Major deposits of nickel ores, either oxidic or sulfidic are located in Australia, Canada, Cuba, Indonesia, New Caledonia, and Russia. Readers are referred to monographs and reviews for detailed discussions of the metallurgy, chemistry, environmental chemistry, biochemistry, toxicology, and biological monitoring of nickel [1–12].

Exposure to nickel compounds can produce a variety of adverse effects on human health. Nickel allergy in the form of contact dermatitis is the most common reaction. Although the accumulation of nickel in the body through chronic exposure can lead to lung fibrosis, cardiovascular and kidney diseases, the most serious concerns relate to nickel's carcinogenic activity which is reviewed below in more detail in regard to its human epidemiology, experimental animal models, and postulated molecular mechanisms.

…

adenocarcinomas (6%), transitional cell carcinomas (3%), and other malignant tumors (4%). The 259 lung tumors examined were diagnosed as squamous cell carcinomas (67%), anaplastic, small cell, and oat

[81]. Nonetheless, as shown by Pikalek and Necasek [82], Ni(II) chloride at higher, relatively toxic concentrations (36–50 mg/l), was markedly mutagenic in a strain of *Corynebacterium* sp. 887 (*hom*).

In contrast to its weak mutagenicity in microbial cells, nickel efficiently transforms human and rodent cells [83–86]. Fibroblastic and epithelial cells were transformed by soluble and insoluble nickel compounds. In rodent cells, in which transformation is achieved more easily than in human cells, the insoluble compounds acted like complete carcinogens.

Besides occupational exposures, nickel released internally from endoprostheses, bone-fixing plates and screws, and other medical devices made of nickel-containing alloys, has been suspected, but not proven, to be the major cause of sporadic local tumors [31,32]. Overall, "implanted foreign bodies consisting of metallic cobalt, metallic nickel, and a particular alloy powder consisting of 66–67% nickel, 13–16% chromium and 7% iron" have been recently classified as "possibly carcinogenic to humans" (Group 2B) by the IARC Committee on Surgical Implants and other Foreign Bodies [33].

5. Search for molecular mechanisms of nickel carcinogenesis

5.1. Uptake, distribution, and retention of nickel

The marked differences in the carcinogenic activities of various nickel compounds most likely reflect the differences in their uptake, transport, distribution and retention, and ultimately—the capacity to deliver Ni(II) ions to specific cells and target molecules. This, in turn, strongly depends on the physical and chem-

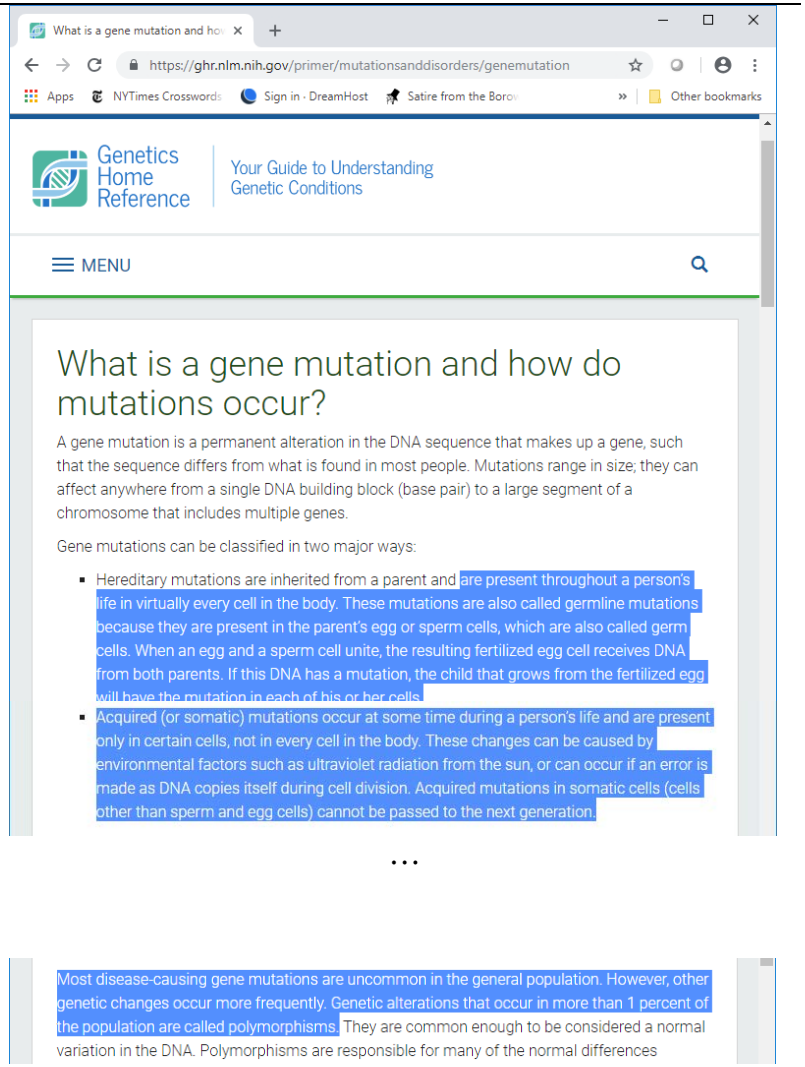
In experimental animals, nickel compounds induce tumors at virtually all sites of application (reviewed in refs. [1,2,4,5,28]). The carcinogenic activity depends strongly on the solubility of the nickel compounds in water and tissue fluids. As a rule, insoluble compounds, such as NiS, NiO, and Ni_3S_2, are better carcinogens than soluble compounds, Ni(II) acetate, chloride, or sulfate. The routes of administration that were shown to produce tumors include inhalation, intramuscular (i.m.), intrarenal (i.r.), intraperitoneal, intraocular (i.o.), subcutaneous (s.c.), and the intra-articular space (i.a.).

[446] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 8-9; **copied without attribution from:** Kasprzak, K.S., Sunderman, F.W. and Salnikow, K. Nickel carcinogenesis. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 533(1):67-97, 2003. (p. 68).

[447] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 9; **copied without attribution from:** Kasprzak, K.S., Sunderman, F.W. and Salnikow, K. Nickel carcinogenesis. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 533(1):67-97, 2003. (p. 72).

[448] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 9; **copied without attribution from:** Kasprzak, K.S., Sunderman, F.W. and Salnikow, K. Nickel carcinogenesis. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 533(1):67-97, 2003. (p. 69).

"Inherited mutations are passed down from parent to child and are present throughout a person's life in virtually every cell in the body. These mutations are also called germline mutations because they are present in the parent's egg or sperm (germ) cells. When an egg and a sperm cell unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the child that grows from the fertilized egg will have the mutation in each of his or her cells."
Acquired (or somatic) mutations occur at some time during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, chemical exposure, or can occur if an error is made as DNA copies itself during cell division. Acquired mutations in somatic cells (other than sperm and egg cells) cannot be passed to the next generation."
"Most disease-causing gene mutations are uncommon in the general population. However, other genetic changes occur more frequently. Genetic alterations that occur in more than 1 percent of the population are called polymorphisms."[449]

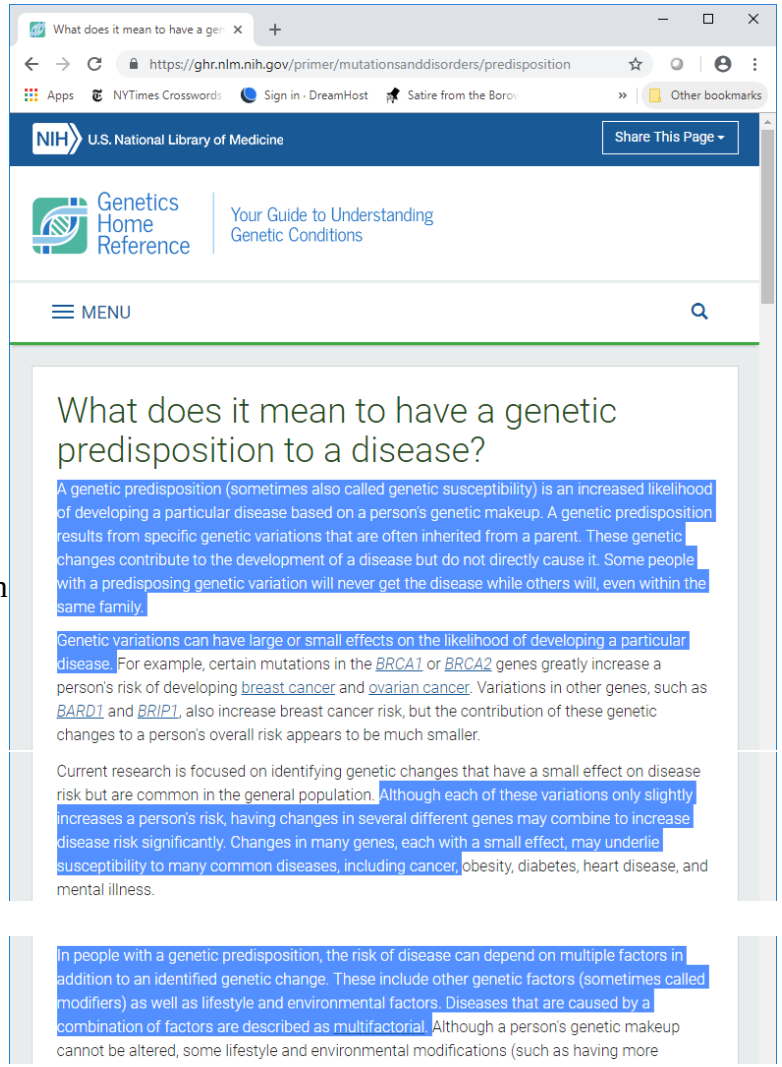


[449] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 18; **copied without attribution** from: https://ghr.nlm.nih.gov/primer/mutationsanddisorders/genemutation, accessed 1/29/19.

"A genetic predisposition (sometimes also called genetic susceptibility) is an increased likelihood of developing a particular disease based on a person's genetic makeup. A genetic predisposition results from specific genetic variations that are often inherited from a parent. These genetic changes contribute to the development of a disease, but do not directly cause it. For example, mutations in the BRCA gene result in an increased risk for ovarian cancer. Some people with a predisposing genetic variation will never get the disease while others will, even within the same family. Genetic variations can have large or small effects on the likelihood of developing a particular disease."

"Although each of these variations only slightly increases a person's risk, having changes in several different genes may combine to increase disease risk significantly. Changes in many genes, each with a small effect, may underlie susceptibility to many common diseases, including cancer."

"In people with a genetic predisposition, the risk of disease can depend on multiple factors in addition to an identified genetic change. These include other genetic factors (sometimes called modifiers) as well as lifestyle and environmental factors. Diseases that are caused by a combination of factors are described as multifactorial."[450]



[450] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 18; **copied without attribution** from https://ghr.nlm.nih.gov/primer/mutationsanddisorders/predisposition, accessed 1/29/19.

Table 12: Dr. Levy copied background information without attribution to the author:

"At its fundamental level, cancer is caused by changes (mutations) to the DNA within cells. The DNA that makes up our genetic code is organized into a large number of individual genes, each of which contains a specific subset of instructions telling the cell what functions to perform, as well as how to grow and divide. Errors in the instructions can cause the cell to stop its normal function and may allow a cell to become cancerous."[451]	https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588 Causes Cancer is caused by changes (mutations) to the DNA within cells. The DNA inside a cell is packaged into a large number of individual genes, each of which contains a set of instructions telling the cell what functions to perform, as well as how to grow and divide. Errors in the instructions can cause the cell to stop its normal function and may allow a cell to become cancerous.
"DNA repair genes look for errors in a cell's DNA and make corrections. A mutation in a DNA repair gene may mean that other errors aren't corrected, leading cells to become cancerous"[452]	https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588 • **Make mistakes when repairing DNA errors.** DNA repair genes look for errors in a cell's DNA and make corrections. A mutation in a DNA repair gene may mean that other errors aren't corrected, leading cells to become cancerous.

[451] Expert Report of Shawn Levy, PhD, 11/16/18, p. 3; **copied without attribution** from https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588, Exhibit 9, Deposition of Shawn Levy, PhD, 1/11/19.
[452] Expert Report of Shawn Levy, PhD, 11/16/18, p. 4; **copied without attribution** from https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588, Exhibit 9, Deposition of Shawn Levy, PhD, 1/11/19.

Table 13: Direct comparison of similar and uncited text from expert reports by Drs. Levy and Zelikoff:

Dr. Levy:	**Dr. Zelikoff:**
"Both inherited and acquired gene mutations work together to cause cancer… Even if one has inherited a genetic mutation that predisposes one to cancer, that doesn't mean he or she is certain to get cancer. Rather, one or more additional gene mutations may be needed to cause cancer. The inherited gene mutation could instead make one more likely to develop cancer when exposed to a certain cancer-causing substance."[453]	"Both inherited and acquired gene mutations work together to cause cancer. Even if one has inherited a genetic mutation that predisposes one to cancer, that doesn't mean he or she is certain to get cancer. Rather, one or more additional gene mutations may be needed to cause cancer. The inherited gene mutation could instead make one more likely to develop cancer when exposed to certain cancer-causing substances."[454]

[453] Expert Report of Shawn Levy, PhD, 11/16/18, p. 5.
[454] Expert Report of Judith Zelikoff, PhD, 11/16/18, p. 20.

H. CONCLUSIONS

Scientific literature does not support a causal relationship between perineal talc use and ovarian cancer. The theory that asbestos, as an alleged contaminant in talc, causes ovarian cancer in women is also unsupported by scientific data. The alleged metal contaminants (chromium, cobalt and nickel) have not been associated with ovarian cancer in animals or humans; human exposure to these earth metals is ubiquitous; and there are no scientific data supporting the concept that alleged trace levels of chromium, cobalt and/or nickel cause ovarian cancer. My review did not support the concept that fragrance ingredients used in Johnson's Baby Powder or Shower to Shower cause ovarian cancer either. These opinions are based on my review of case materials; review and analysis of published literature; and application of fundamental toxicology principles, including consideration of both hazard and dose.

Because every agent presents an inherent hazard to human health at a sufficiently high dose (e.g., even water can be lethal when ingested in sufficient quantity), toxicologists do not use hazard identification statements alone, without knowledge, analysis and assessment of exposure levels associated with adverse effects when estimating the risk of adverse effects to a population.

To the extent additional information becomes available, I may modify or add to the above opinions.

I. ATTACHMENTS

- Attachment 1: CV
- Attachment 2: Testimony List

ATTACHMENT 1

TO THE RULE 26 REPORT OF
H. NADIA MOORE, PH.D., DABT, ERT

CV

VERITOX®

Nadia Moore, PhD, DABT, ERT

Principal Toxicologist

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Education

Ph.D., Toxicology, University of Washington, Seattle WA, 2008

B.S., Chemistry, Pacific Lutheran University, Tacoma, WA, 1992

Certifications

Diplomate of the American Board of Toxicology, 2012-present

Registered Toxicologist (United Kingdom and EUROTOX registries), 2015-present

NIOSH Spirometry Testing Certification, 2015-2017

Project Management Professional, 2011-2014

Professional Affiliations and Associated Appointments

American Board of Toxicology

Society of Toxicology (SOT), Full member

- Inhalation and Respiratory Specialty Section member
- Nanotoxicology Specialty Section member
- Women in Toxicology Interest (WIT) Group member; WIT Councilor (2016-2018 term)
- Pacific Northwest Association of Toxicologists (PANWAT) member
  - PANWAT Councilor (2014-2016 term); Vice President Elect (2016-2017 term); Vice President (2017-2018 term); President (2018-2019 term)

American College of Toxicology (ACT), Full member

British Toxicology Society (BTS), Member

American College of Occupational and Environmental Medicine (ACOEM), Associate member

American Association for the Advancement of Science (AAAS), Member

American Conference of Governmental Industrial Hygienists (ACGIH), Voting member

American Chemical Society (ACS), Member

American Industrial Hygiene Association (AIHA), Full member

Society for Experimental Biology and Medicine (SEBM), Associate member

Hope (Nadia) Moore, PhD, DABT, ERT

Other Professional Activities

Practicing Scientist Member, Institutional Animal Care and Use Committee (IACUC) Pacific Northwest National Laboratory, Sequim Laboratory, and the Columbus-based Toxicology Laboratory (ToxNW), 2011 - 2013

Invited lecturer, Fundamentals of Toxicology Graduate Course ENVH514, University of Washington (Lung: Structure, Function, Absorption, & Inhalation)

Invited reviewer, Food and Chemical Toxicology (Elsevier Sciences), Human and Experimental Toxicology (Sage Journals), NeuroToxicology (Elsevier Sciences), Toxicology Letters (Elsevier Sciences), and Toxicological Sciences (Oxford Journals)

Platform Session Chairperson, Persistent Organic Pollutants Platform Session, Society of Toxicology 57th Annual Meeting, San Antonio, TX.

Experience

2018 - Present	**Veritox®, Inc.** *Principal Toxicologist*	**Redmond, Washington**
2013 - 2018	**Veritox®, Inc.** *Senior Toxicologist*	**Redmond, Washington**
2008-2013	**Battelle Toxicology Northwest** *Pharmacologist / Safety Toxicologist*	**Richland, Washington**
2003-2008	**University of Washington** *Toxicology Doctoral Student / Teaching Assistant / Research Assistant*	**Seattle, Washington**
2001-2003	**Battelle Pacific NW National Laboratory** *Senior Research Scientist*	**Richland, Washington**
2000-2001	**Battelle Toxicology Northwest** *Principal Research Scientist*	**Richland, Washington**
1992-2000	**Battelle Toxicology Northwest** *Research Scientist / Technical Specialist /Technician*	**Richland, Washington**

Professional Honors

National Toxicology Program Toxicology Discipline Leader Battelle Toxicology Northwest, Richland, WA (2011-2013)

Outstanding Performance Award in recognition of Outstanding Efforts as Study Director. Battelle Toxicology Northwest, Richland, WA (2009)

Pre-Doctoral Fellow National Institute of Environmental Health Sciences Environmental Pathology and Toxicology Training Grant.
University of Washington, Seattle, WA (2005-2008)

Outstanding Student Poster Award Recipient from the PANWAT (Pacific Northwest Association of Toxicologists, Regional Chapter of the Society of Toxicology) Annual Meeting (2007)

Student Merit Meeting Award Recipient from the Research Society on Alcoholism, 30th Annual Meeting of the Research Society on Alcoholism, Chicago, IL (2007)

Hope (Nadia) Moore, PhD, DABT, ERT

Selected Publications

TJ Mast, F Adeshina, N Moore, H Choudhury, A Protzel, and A Mahfouz. 2002. Identification of common toxic effects with common mechanisms of toxicity for pesticides selected from the drinking water contaminant list (CCL). *The Toxicologist,* Supplement to Toxicological Sciences, 66(1):494.

F Adeshina, T Mast, N Moore, A Mahouz, A Protzel, and H Choudhury. 2003. Identifying triazine herbicides on EPA drinking water contaminant candidate list (CCL) for common mechanism of toxicity and cumulative risk assessment. *The Toxicologist,* Supplement to Toxicological Sciences, 72(1):436.

N Moore, M Guizzetti, B Gallis, S Shaffer, DR Goodlett, and LG Costa. 2006. Use of proteomic approaches for the identification of changes in astrocyte secretion following ethanol exposure. *The Toxicologist,* Supplement to Toxicological Sciences, 90(1):1437.

M Guizzetti, G Giordano, N Moore, and LG Costa. 2008. Ethanol inhibits hippocampal neuron differentiation induced by carbachol-treated astrocytes. *The Toxicologist,* Supplement to Toxicological Sciences, 102(1):1963.

M Guizzetti, NH Moore, G Giordano, and LG Costa. 2008. Modulation of neuritogenesis by astrocyte muscarinic receptors. *J. Biol. Chem.* 283(46): 31884-31897.

N Moore, M Guizzetti, G Giordano, and LG Costa. 2008. Ethanol inhibits muscarinic receptor-induced release by astrocytes of extracellular proteins involved in neuronal development. *The Toxicologist,* Supplement to Toxicological Sciences, 102(1):1964.

NH Moore, LG Costa, SA Shaffer, DR Goodlett, and M Guizzetti. 2009. Shotgun proteomics implicates extracellular matrix proteins and protease systems in neuronal development induced by astrocyte cholinergic stimulation. *J. Neurochem.* 108(4):891-908.

M Guizzetti, NH Moore, G Giordano, KL VanDeMark, and LG Costa. 2010. Ethanol inhibits neuritogenesis induced by astrocyte muscarinic receptors. *Glia.* 58(12):1395-406.

M Guizzetti, NH Moore, KL VanDeMark, G Giordano, and LG Costa. 2011. Muscarinic receptor-activated signal transduction pathways involved in the neuritogenic effect of astrocytes in hippocampal neurons. *Eur. J. Pharmacol*. 659(2-3):102-7.

CY Chan, LJ Swenson, J Hobden, N Moore, and BJ Kelman. 2014. Risk from exposure to triorthocresyl phosphate (TOCP) in aircraft cabins and flight decks. *The Toxicologist,* Supplement to Toxicological Sciences, 138(1):2247.

BC Sayers, MD Stout, MF Cesta, N Moore, GL Baker, KM Patton, BK Hayden, JA Dill, and NJ Walker. 2014. Thirty-day whole-body inhalation toxicity and tissue burden study of multiwalled carbon nanotubes in Harlan Sprague-Dawley rats and B6C3F1 mice. *The Toxicologist,* Supplement to Toxicological Sciences, 138(1):2004A.

N Moore, CY Chan, M Krause, and BJ Kelman. 2015. Risk from traffic-related air pollution in schools: beyond distance to roadway. 2015. *The Toxicologist,* Supplement to Toxicological Sciences, 149(1):577.

CY Chan, M Krause, B Kelman, and N Moore. 2016. Risk from breaches in portable, consumer sized lithium batteries. *The Toxicologist,* Supplement to Toxicological Sciences, 150(1):2671.

B Kelman, R Evoy, C Chan and N Moore. 2016. Fluoride: friend or foe. *The Toxicologist,* Supplement to Toxicological Sciences, 150(1):2277.

N Moore, B Hardin, C Robbins, and B Kelman. 2016. Smoker's Risk of Lung Cancer from Asbestos Exposure. *The Toxicologist,* Supplement to Toxicological Sciences, 150(1):2696.

BA Magnuson, MC Carakostas, NH Moore, SP Poulos, and AG Renwick. 2016. Biological fate of low calorie sweeteners. *Nutr Rev*. 74(11):670-689.

JA Deyo, KA Tucker, CY Chan, NH Moore, and BJ Kelman. 2017. Marijuana: the smoke hasn't cleared. *The Toxicologist,* Supplement to Toxicological Sciences, 156(1):1282.

BJ Kelman, CY Chan, NH Moore, and LC Diener. 2017. Weight-of-evidence assessment for polyhexamethylene guanidine and interstitial lung disease. *The Toxicologist,* Supplement to Toxicological Sciences, 156(1):1287.

C Chan, K Tucker, N Moore, and B Kelman. 2018. Risk from Mycotoxins in Mold-Infested Consumer Products. *The Toxicologist,* Supplement to Toxicological Sciences, 162(1):2407.

Selected Continuing Education

Analytical Validation for the Pharmaceutical Industry, American Association of Pharmaceutical Scientists (AAPS). AAPS Workshop on Current Issues, Arlington, VA, 1998.

Bioanalytical Methods Validation – A Revisit with a Decade of Progress. Co-sponsored by AAPS and FDA, Arlington, VA, 2000.

GLP Essentials for Technical Staff. Debi Garvin, Instructor, West Coast Quality Training Institute, Richland, WA, 2001.

A Practical Approach to Blood and Lymphoid Tissue (BLT) in Toxicology Assessments. JCL Schuh and L Lanning, Chairpersons. Society of Toxicology Continuing Education Course, Nashville, TN, 2002.

Good Laboratory Practices for Study Directors and Monitors. D Garvin, Instructor and Director, West Coast Quality Training Institute, Hood River, OR, 2008.

Introduction to Good Laboratory Practice Regulations. D Garvin, Instructor and Director, West Coast Quality Training Institute, Hood River, OR, 2008.

Primer in Pathology: Interpreting and Integrating Nonclinical Study Results. Continuing Education Course. Pacific Northwest Chapter of the Society of Toxicology, Pacific Northwest Association of Toxicologists Annual Meeting, Seattle, WA, 2009.

Stress as a Confounding Factor in Toxicology Studies. K Sprugel and N Everds, Chairpersons. Society of Toxicology Continuing Education Course, Baltimore, MD, 2009.

Immunology for Toxicologists. R Pieters and I Kimber, Chairpersons. Society of Toxicology Continuing Education Course, Baltimore, MD, 2009.

Integrative Toxicity Test Methods to Improve Hazard Identification. Society of Toxicology Pacific Northwest Chapter, Pacific Northwest Association of Toxicologists Annual Meeting, Corvallis, OR, 2010.

Segment-Specific Renal Pathology for the Non-Pathologist. D Hoivik and SG Emeigh Hart, Chairpersons. Society of Toxicology Continuing Education Course, Salt Lake City, UT, 2010.

Evaluating Toxicity of Engineered Nanomaterials: Issues with Conventional Toxicology Approaches. SS Nadadur and FA Witzmann, Chairpersons. Society of Toxicology Continuing Education Course, Washington DC, 2011.

Current Nonclinical Strategies and Methods for Evaluating Drug-Induced Cardiovascular Toxicity. H Wang and DJ. Murphy, Chairpersons. Society of Toxicology Continuing Education Course, Washington DC, 2011.

Northwest Association for Biomedical Research IACUC Education Conference, Seattle, WA, 2011.

Art and Science of Research Translation in Toxicology. Society of Toxicology Pacific Northwest Chapter, Pacific Northwest Association of Toxicologists Annual Meeting. North Bonneville, WA, 2011.

Mid America Toxicology Course, CD Klaassen, Course Director, Kansas City, MO, April 2012.

The What, When, and How of Nonclinical Support for an IND Submission. P Nugent and D Colagiovanni, Chairpersons. Society of Toxicology Continuing Education Course, San Antonio, TX, 2013.

Understanding Toxic Neuropathy in Drug Development: Both Clinical and Nonclinical Perspectives. MJ Kallman and J Benitez, Chairpersons. Society of Toxicology Continuing Education Course, San Antonio, TX, 2013.

Innovations in Methodologies for Inhalation Exposures and Interpretations of In Vivo Toxicity, Urmila Kodavanti and Juergen Pauluhn, Chairpersons. Society of Toxicology Continuing Education Course, Phoenix, AZ, 2014.

Methodologies in Human Health Risk Assessment, Qiyu (Jay) Zhao and M.E. (Bette) Meek, Chairpersons. Society of Toxicology Continuing Education Course, Phoenix, AZ, 2014.

Advances in Safety Assessment of Medical Devices, Niranjan S Goud and Ron Brown, Chairpersons. Society of Toxicology Continuing Education Course, San Diego, CA, 2015.

New Horizons in Chemical Carcinogenesis: Advances in Mode of Action and Mechanism of Cancer Pathogenesis, James E Klaunig and Udayan M Apte, Chairpersons. Society of Toxicology Continuing Education Course, San Diego, CA, 2015.

The New World of Cancer Immunotherapy: Challenges in Bench to Bedside Translation, Rodney Prell and Rafael A Ponce, Chairpersons. Society of Toxicology Continuing Education Course, San Diego, CA, 2015.

OECD GLP and Documentation Training Course, Robin Guy and Dave Hobson, Instructors. Robin Guy Consulting, Morristown, NJ, Aug. 31 – Sept. 1, 2015.

Nanomaterials, Chemical Exposures and Control Banding: What Does It Mean for Workplace Safety? University of Washington Continuing Education Programs, hosted by the Pacific Northwest Section – American Industrial Hygiene Association. Oct. 14, 2015

NIOSH-Approved 2-Day Initial Spirometry Training Course, Martha Horike-Pyne, Instructor. University of Washington Continuing Education Programs, Seattle WA. Nov. 7-8, 2015.

Advancing the Detection, Imaging, and Pitfalls in Monitoring Oxidative Stress in Health and Disease. Maria B. Kadiiska and Ronald P. Mason, Chairpersons. Society of Toxicology Continuing Education Course, New Orleans, LA, 2016.

Basic Principles and Practices for Applying Epigenetics in Mechanistic Toxicology. Shaun D. McCullough and Ronald N. Hines, Chairpersons. Society of Toxicology Continuing Education Course, New Orleans, LA, 2016.

Human Health Risk Assessment: A Case Study Application of Principles. John C. Lipscomb and M.E. (Bette) Meek, Chairpersons. Society of Toxicology Continuing Education Course, New Orleans, LA, 2016.

Adding Up Chemicals: Component-Based Risk Assessment of Chemical Mixtures. Jane Ellen Simmons and Richard C. Hertzberg, Chairpersons. Society of Toxicology Continuing Education Course, Baltimore, MD, 2017.

Extrapolation in the Airways: Strategies to Incorporate *In Vivo* and *In Vitro* Data to Better Protect Human Health. Marie C. Fortin and Madhuri Singal, Chairpersons. Society of Toxicology Continuing Education Course, Baltimore, MD, 2017.

In Vitro Testing: Tales from the Real World. Kelly P. Coleman and Amy J. Clippinger, Chairpersons. Society of Toxicology Continuing Education Course, San Antonio, TX, 2018.

The What, When, and How of Using Data from Alternative Testing Methods in Chemical Safety Assessments. Suzanne C. Fitzpatrick and Mansi Krishan, Chairpersons. Society of Toxicology Continuing Education Course, San Antonio, TX, 2018.

Uncertainty Characterization in 21st-Century Toxicology: Current Practice and Practical Methods Supporting Regulatory Risk Assessment. Kristi Muldoon-Jacobs and Andrea Richarz, Chairpersons. Society of Toxicology Continuing Education Course, San Antonio, TX, 2018.

ATTACHMENT 2

TO THE RULE 26 REPORT OF
H. NADIA MOORE, PH.D., DABT, ERT

Testimony List

Testimonies Given By
Hope (Nadia) Moore, PhD, DABT, ERT

Oakland Bulk and Oversized Terminal, LLC vs. City of Oakland
United States District Court, Northern District of California, San Francisco Division
Case No. 3:16-cv-07014-VC
Deposition: November 7, 2017
Trial testimony: January 19, 2018